Basal Insulin Adjustments and Continuous Glucose Monitoring During Exercise in Type 1 Diabetes

DESSI P. ZAHARIEVA

A DISSERTATION SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN KINESIOLOGY AND HEALTH SCIENCES
YORK UNIVERSITY
TORONTO, ONTARIO

December 2018

Abstract

Research has demonstrated that the timing, type, duration and intensity of exercise can all impact blood glucose levels differently in patients with type 1 diabetes. Continuous steady state moderate intensity 'aerobic' exercise tends to drop blood glucose levels, while vigorous-to-maximal intensity exercise tends to cause blood glucose levels to rise. The purpose of this dissertation was to test different basal insulin strategies to improve glycemia during various forms of exercise and in recovery in patients with type 1 diabetes on continuous subcutaneous insulin infusion (CSII) therapy. A secondary purpose was to examine the effectiveness of continuous glucose monitor (CGM) technology to track interstitial glucose levels during exercise and in recovery.

Initially, we examined the effects of insulin pump suspension on glycemia during aerobic and circuit-based exercise. We found that pump suspension at exercise onset caused a greater drop in glycemia during aerobic vs. circuit-based exercise. Aerobic exercise also modestly increased the time spent in hypoglycemia 12 hours post-exercise. We then investigated the effects of a reduced insulin infusion rate ('pump on') vs. pump suspension ('pump off') during intermittent high intensity exercise and found neither an advantage nor disadvantage on blood glucose level with pump removal for exercise. Interestingly, 'pump on' resulted in slightly higher time spent in hypoglycemia in the 12-hour period post-exercise vs. 'pump off'.

In a third study, we tested the strategy of lowering basal insulin delivery by 50% or 80% well in advance of exercise vs. pump suspension at exercise onset in an attempt to reduce hypoglycemia risk. Overall, we found that a 50-80% basal rate reduction set 90 mins pre-exercise attenuated the drop in blood glucose level better than pump suspension at exercise start. Finally, we assessed CGM accuracy during exercise and in the meal post-exercise and found that

CGM underestimated the drop in glycemia during exercise and appeared to lag behind self-monitoring blood glucose values when glycemia was changing rapidly.

This thesis dissertation highlights a number of novel strategies, including basal insulin rate reductions and altering the type of exercise for improved exercise management in people living with type 1 diabetes on CSII.

Acknowledgements

To the person I hold in highest regard, my supervisor, Dr. Michael Riddell. I remember when I first started as an MSc student in your lab, you were unsure if you had made the right choice. Not because of my abilities, but because you understood that living with type 1 diabetes, researching type 1 diabetes, speaking and educating other people about type 1 diabetes can be overwhelming because you never really get a break from it. After all of these years by your side, I hope you know that you made the right decision! Thank you for believing in me, even when I did not believe in myself. Thank you for taking me under your wing and guiding me, and always teaching me how to be a critical thinker. From you, I have learned that we should always try new things - for the love of science and life. I will always be here to help you with your technology problems and to make sure you don't miss any flights, important meetings, or family events. Diabetes related or not, I know that I can always turn to you for advice and support. You truly have changed my life forever, thank you.

I would like to express my sincerest gratitude to all of my committee members, Drs. Veronica Jamnik, Heather Edgell, Gary Sweeney, & Jane Yardley. Thank you for sharing your knowledge and expertise with me over the years and for taking the time to read and provide insight on my thesis.

To the past and present 'Riddell Lab' members, you know who you are. Thank you for making this entire journey so memorable. You have all taught me so much over the years and I could not have done this without you. Thank you to all of the research participants and my friends in the diabetes community, you are more like family! I was fortunate enough to receive the Vanier Canada Graduate Scholarship during my doctoral studies and I am forever appreciative for this financial support throughout my academic career.

I would like to thank my parents, my brother, and the rest of my family and friends for their constant support and encouragement throughout these many years as a graduate student. Danny, thank you for watching over me and being my guiding light. Mom and dad, you both taught me from a young age the importance of finding passion in your career. Not only do I love my work, but I also get the chance to help people of all ages living with type 1 diabetes to be more physically active and improve their diabetes management.

Last but not least, I would like to say 'благодаря' to my rock and best friend, Adam. You are the most stable and grounded person in my life and I would not have reached the finish line without you by my side. Thank you for always being patient with me and for cheering me up when I needed it most. I am forever grateful.

Table of Contents

List of Tables

1.0 Review of the Literature

3.0 Academic Paper #1

4.0 Academic Paper #2

5.0 Academic Paper #3

6.0 Academic Paper #4

List of Figures

1.0 Review of the Literature

3.0 Academic Paper #1

4.0 Academic Paper #2

5.0 Academic Paper #3

6.0 Academic Paper #4

List of Appendices

List of Abbreviations

ACSM – American College of Sports Medicine

ADA – American Diabetes Association

ANOVA – analysis of variance

ATP – adenosine triphosphate

BG – blood glucose

BRR – basal rate reduction

CGM – continuous glucose monitoring

CHO - carbohydrates

CON – continuous, steady state exercise

CIRC – circuit-based exercise

CSII – continuous subcutaneous insulin infusion

DCCT – Diabetes Control and Complications Trial

EE – energy expenditure

ELISA – enzyme-linked immunosorbent assay

FGM – flash glucose monitor

GLUT-4 – glucose transporter 4

GMI – glucose management indicator

GV – glucose variability

HAAF – hypoglycemia-associated autonomic failure

HbA_{1c} or A1c – hemoglobin A_{1c}

HCL – hybrid closed-loop

HR – heart rate

IPAQ – international physical activity questionnaire

ISPAD - International Society for Pediatric and Adolescent Diabetes

Kcal – kilocalories

MARD – mean absolute relative difference

MDI – multiple daily injections

MET – metabolic equivalent

PA – physical activity

PAR-Q+ – physical activity readiness questionnaire for everyone

PCr - phosphocreatine

rtCGM – real-time continuous glucose monitor

SD – standard deviation

SEM – standard error of the mean

SMBG – self-monitoring of blood glucose

T1D – type 1 diabetes

TDD – total daily insulin dose

VO_2max – maximal oxygen consumption

VO_2peak – peak oxygen consumption

YSI – yellow springs instrument

1.0 INTRODUCTION & REVIEW OF THE LITERATURE

1.0 Introduction & Background

Type 1 diabetes is an autoimmune disease characterized by the absolute destruction of insulin producing beta (β) cells (1). Without β-cells to produce endogenous insulin, the body experiences excursions in glycemia that are outside of the physiological range. Therefore, for the management of type 1 diabetes, patients require exogenous insulin administration via multiple daily injections or insulin pump therapy and frequent self-monitoring of blood glucose (SMBG) using traditional fingerstick capillary sampling and a handheld glucose meter (2).

Regular physical activity has been shown to have many health benefits for individuals with type 1 diabetes including reduced cardiovascular disease risk factors (3), improvements in insulin sensitivity (4), and overall wellbeing (5). However, exercise and physical activity can also cause dramatic, and sometimes dangerous, excursions in blood glucose concentration, thereby increasing the complexity and challenges involved with overall glycemic control. Despite the recommendations for individuals with type 1 diabetes to engage in regular physical activity, the exact type of training and insulin adjustments required to maintain blood glucose levels in a target range is up for debate. For patients with type 1 diabetes, many factors need to be taken into consideration prior to engaging in physical activity and exercise such as the timing, duration, and intensity of exercise, possible adjustments in basal insulin rates, nutrition, and the amount of active or 'on-board' insulin present at the onset of exercise. If these factors are ignored and not managed accordingly, there is an increased risk of developing hypoglycemia or hyperglycemia during activity. Maintaining a blood glucose concentration between 6.0-8.0 mmol/L (108-144 mg/dL) during activity is believed by some to be the 'optimal blood glucose range' for exercise performance in adolescents with type 1 diabetes (6); however, whether this range applies to all patients and for all settings of physical activity and exercise is currently

unknown. Nonetheless, this is something that most patients with type 1 diabetes strive for during physical activity and exercise, but often with very limited success.

With advancements in technology such as continuous glucose monitor (CGM) devices, patients can wear a glucose sensor subcutaneously that is connected to a transmitter and monitors interstitial glucose level over 24 hours. CGM devices also provide information on the directional rate of change in interstitial glucose and can be extremely beneficial before, during, and after an exercise session. Real-time CGM (rtCGM) devices are also extremely valuable because they can be used to alert patients of an impending hypo- or hyperglycemic event (7), for example during aerobic exercise that is often associated with declines in glycemia and subsequently can lead to hypoglycemia (8). Using rtCGM, studies are now better able to monitor glucose variability, fluctuations, and recurring trends in glycemia.

1.1 Physiology of physical activity and exercise

1.1.1 Exercise modalities

Although the terms 'physical activity' and 'exercise' have many similarities and are often used interchangeably, there are slight differences worth distinguishing. Physical activity is described as any movement carried out by the skeletal muscles that results in an increase in energy expenditure relative to the resting state (i.e. sitting or lying down) (9). Physical activity is often expressed in kilocalories (kcals). Energy expenditure is often estimated by the volume of activity (i.e. light, moderate, vigorous, and vigorous-to-maximum) per minute, relative to body mass (10) and is expressed in kilojoules or kilocalories. Exercise, however, is a planned, repetitive, and structured movement that aims to improve physical fitness (11).

The human body uses three main energy sources to maintain homeostasis and these include immediate, oxidative, and non-oxidative energy sources (12). Activities are often simplistically classified as being either 'aerobic' (oxidative) or 'anaerobic' (non-oxidative) in nature; however, most activities rely on the interplay between both oxidative and non-oxidative energy sources (13). Aerobic exercises are generally continuous steady state light-moderate-vigorous intensity, rhythmic movements using large muscle groups such as brisk walking, light jogging, cycling, and recreational swimming (14). Light-to-moderate intensity physical activity is generally associated with an intensity between 3–6 metabolic equivalents (METs), or ~50–75% of an individual's age-predicted maximum heart rate (10). Mixed or circuit-based activities are still aerobic in nature and sometimes referred to as high intensity interval or intermittent activities. More specifically, these are light-to-moderate intensity activities interspersed with intermittent, moderate-to-vigorous and vigorous-to-maximal intensity bouts. Individual and team sports (e.g. baseball, basketball, tennis, soccer, etc.) or interval training are some examples of

mixed activities. During mixed activities, these high intensity workloads can reach 6-10 METs or approximately 75–100% of an individual's maximum heart rate (15). Resistance exercises are often more brief, repetitive movements that incorporate weights, weight machines, resistance bands, or simply one's own body weight (14). During intense muscle contractions, there is a greater reliance on muscle phosphagens [adenosine triphosphate (ATP) and phosphocreatine (PCr)] and anaerobic glycolysis and these types of activities tend to cause a more dramatic rise in glucose counterregulatory hormones (catecholamines, glucagon, cortisol, and growth hormone) (16).

1.1.2 Common terminology misclassifications

Traditionally, activities that last a few seconds up to one minute are often described as 'anaerobic' and activities that are two minutes or longer are predominantly 'aerobic' (12). However, in this section, these words will be explained in further detail and we will highlight how this terminology is often misrepresented in sports medicine and academia.

Specifically, at lower intensities and continuous steady state activity, aerobic metabolism is the dominant system. The key source of energy provision during continuous steady state exercise is plasma free fatty acids (15). Conversely, it has been argued that 'oxidative phosphorylation' more accurately describes activities that are 'aerobic' in nature as most activities are not purely dependent on one single energy system. As the intensity of exercise increases and energy demands rise, there is a greater interplay of ATP-PCr and glycolysis energy systems. At very intense contraction rates, plasma glucose uptake and utilization is minimal and the primary fuel is muscle phosphocreatine and muscle glycogen (15). Another important distinction is that 'anaerobic' metabolism is a pathway that functions 'independent of oxygen' rather than being referred to it as working 'in the absence of oxygen' (17). More importantly and

often overlooked, is that maximal sprints or exercises lasting less than 30 seconds still have a small aerobic component during the activity and oxygen consumption can be increased for four or more hours in recovery (18, 19). In the present day, it is accepted that energy provision is a permutation of all three pathways working together, often with one of those systems functioning above the others (20). For the purposes of this thesis dissertation, the term 'aerobic' refers to continuous steady state light-to-moderate intensity exercise and the term 'circuit or intermittent high intensity' exercise refers to light-to-moderate intensity activity interspersed with variable bursts of moderate-vigorous-maximal intensity activity. In addition, activities lasting < 40 minutes will be referred to as 'short' duration exercise, whereas activities that are > 40 minutes will be referred to as 'prolonged' exercise.

1.2 Metabolic responses to structured exercise in non-T1D

1.2.1 Glucose homeostasis during exercise

For individuals without type 1 diabetes, the body is able to maintain blood glucose concentration in a tight range (between 4.0-6.0 mmol/L or 72-108 mg/dL) during exercise through a number of different mechanisms (16). Insulin and glucagon are two of the major hormones responsible for the body's ability to maintain glucose homeostasis at rest and during aerobic exercise. During aerobic exercise, the body begins to break down liver and muscle glycogen stores in order to preserve blood glucose in large part because of the rise in the glucagon-to-insulin ratio (21). Contraction-mediated glucose uptake and use by the skeletal muscles can cause glucose oxidation to increase as much as 10-fold, and circulating blood glucose levels will drop markedly without adjustments to this hormone ratio (21). Specifically, with prolonged, moderate intensity aerobic exercise, these carbohydrate stores are limited and blood glucose concentration may begin to drop even in patients without diabetes if no oral

carbohydrate is ingested (22). To combat this drop in glycemia as muscle glucose uptake is markedly increased, the body responds with a decrease in insulin secretion, a rise in glucagon secretion among other counterregulatory hormones, and an increase in hepatic glucose production to prevent hypoglycemia (23). Following exercise, insulin sensitivity has been shown to persist for up to 48 hours in recovery (24).

During vigorous-to-maximal exercise (> 80% maximum oxygen uptake), the body secretes a number of different counterregulatory hormones such as cortisol, growth hormone, and catecholamines (e.g. epinephrine and norepinephrine) that tend to increase blood glucose concentration above normal levels (25). This type of exercise cannot be maintained for a sustained duration, therefore when catecholamines (specifically epinephrine and norepinephrine) are secreted, this stimulates the liver to release glucose into the circulation beyond what can be utilized by skeletal muscle (21). Vigorous-to-maximal intensity exercise is also associated with drastic elevations in lactate levels, particularly when the rate of lactate production far exceeds lactate oxidation or clearance (26). An increase in counterregulatory hormones and acid-base disturbance is associated with reduced lactate oxidation. This can lead to temporary elevations in blood glucose concentration even in individuals without diabetes, but this phenomenon is further exaggerated in type 1 diabetes (25). Similarly, research suggests that vigorous-to-maximal intensity resistance exercise elicits similar metabolic and hormonal responses (27).

1.3 Type 1 diabetes

Type 1 diabetes is an autoimmune disease caused by the body's destruction of insulin producing beta (β) cells of the pancreas (2). Type 1 diabetes results in complete insulin deficiency and accounts for approximately 5-10% of all diabetes cases (2). Based on the Diabetes Canada 2018 Guidelines, type 1 diabetes is often diagnosed with a fasting plasma

glucose concentration of ≥ 7.0 mmol/L or two hour plasma glucose level ≥ 11.1 mmol/L following a 75 gram oral glucose load (2). Although there is no immediate cure for type 1 diabetes to date, treatment options include the administration of exogenous insulin via multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) using insulin pump therapy. These treatment strategies are used in combination with SMBG using a glucose meter, which is a small, compact device and a glucose test strip that requires a small amount (~ 2-10 μL) of capillary blood usually from the fingertip.

Some common symptoms associated with type 1 diabetes include hypo- and hyperglycemia. Hypoglycemia is used to describe blood glucose concentration ≤ 3.9 mmol/L and can range from feelings of shakiness, irritability, hunger, increased sweating, weakness, and numbness or tingling in the tongue or lips. Hypoglycemia often results from a combination of factors including too little food, too much exercise, and/or too much insulin (2). Hyperglycemia is used to describe a fasting blood glucose concentration > 7.0 mmol/L or ≥ 10.0 mmol/L two-hours postprandial. Symptoms of hyperglycemia may include thirst, frequent urination, and/or fatigue and is commonly a result of too much food, too little insulin, too little exercise, or a combination of these factors (2). In patients with poorly controlled diabetes, chronic hyperglycemia has also been linked to long-term damage of various organs including the kidneys, eyes, blood vessels, and the heart (28).

1.3.1 Glycated Hemoglobin (HbA_{1c})

Glycated hemoglobin, better known as HbA_{1c} or sometimes A_{1c} in the United States of America, is a standard measure of diabetes (glycemic) control over the previous 8-12 weeks (2, 29). The Diabetes Control and Complications Trial (DCCT) was the first large randomized study to correlate higher HbA_{1c} (> 7.0%) values to an increased risk of microvascular and

cardiovascular complications (30). Therefore, the general recommendation for individuals with type 1 diabetes is a target HbA_{1c} level of ≤ 7.0% to reduce the likelihood of complications (30).

The T1D Exchange Clinical Network gathered HbA_{1c} values from over 16,000 patients living with type 1 diabetes and assessed mean HbA_{1c} by year of age (31). This invaluable data showed that the majority of individuals with type 1 diabetes were not maintaining optimal glycemic control and in fact, most 13-17 year olds were well above the recommended guidelines with a mean HbA_{1c} of ~ 9.0% (31). According to this dataset, glycemic control appears to improve and plateau with a mean HbA_{1c} between 7.5-7.8% after the age of 30 (31). It is of concern that even with all of the new technological advancements in diabetes management, very modest improvements in overall diabetes management have occurred over the past 20 years (31).

An ongoing topic of debate is whether exercise training improves HbA_{1c} in type 1 diabetes. Some studies have found that regular structured exercise participation does not markedly improve HbA_{1c} levels in individuals with type 1 diabetes (32-35) and may even be associated with a slight elevation in HbA_{1c} if the activities are frequent and intense (36). Other studies have demonstrated slight improvements in HbA_{1c} with exercise training in both well-controlled (37) and poorly controlled (38, 39) patients with type 1 diabetes, typically by ~0.3-0.5% according to recent meta-analyses with considerable inconsistency among the limited number of studies published to date (40). However, due to considerable differences in measurement devices used, the duration, intensity, type of exercise, and baseline HbA_{1c} levels, this may account for the outcome variation among these exercise-training interventions (40).

One of the limitations of HbA_{1c} is that it fails to capture the variability of glucose, specifically the intra- and inter-day excursions that may lead to extreme hypo- and hyperglycemic events (41, 42). Therefore, more recent studies have focused on incorporating

measures such as glucose variability (GV) and Glucose Management Indicators (GMI) as additional diabetes management tools (42, 43). Both GV and GMI metrics can be calculated from continuous glucose monitoring (CGM) systems that will be discussed in a later chapter.

1.3.2 Exogenous insulin therapy

Individuals with type 1 diabetes are unable to produce endogenous insulin once the β-cells have been destroyed and therefore insulin administration must occur exogenously. Whether individuals with type 1 diabetes are using MDI (insulin pen or syringe) or CSII (insulin pump) therapy, insulin administration varies. Since the discovery of insulin in 1921, insulin formulations have continued to improve (44). Insulin action is often differentiated based on pharmacokinetic and pharmacodynamic properties. Insulin is given in the form of a 'bolus' of rapid-acting insulin analog or short-acting insulin or a 'basal' dose of intermediate-acting or long-acting insulin. Patients that use MDI therapy usually administer both short-acting and long-acting insulin analogues via injections whereas CSII therapy uses an insulin pump device with only short-acting insulin for both continuous basal insulin infusion and bolus insulin infusion. A bolus of insulin is often taken before a meal or to correct hyperglycemia (1). Bolus insulins include insulin aspart (NovoRapid®), glulisine (Apidra®), lispro (Humalog®), faster-acting aspart (Fiasp®), and regular (Humulin®-R). Basal insulins include insulin neutral protamine Hagedorn (Humulin®-N, and Novolin ge®), detemir (Levemir®), glargine (Lantus®, Basaglar®, and Toujeo®), and degludec (Tresiba®), all of which have different pharmacokinetics to cover insulin needs in-between meals and overnight (2). Together, this 'basal-bolus insulin regimen' is trying to mimic the natural physiological response of insulin in individuals without type 1 diabetes (Figure 1.1).

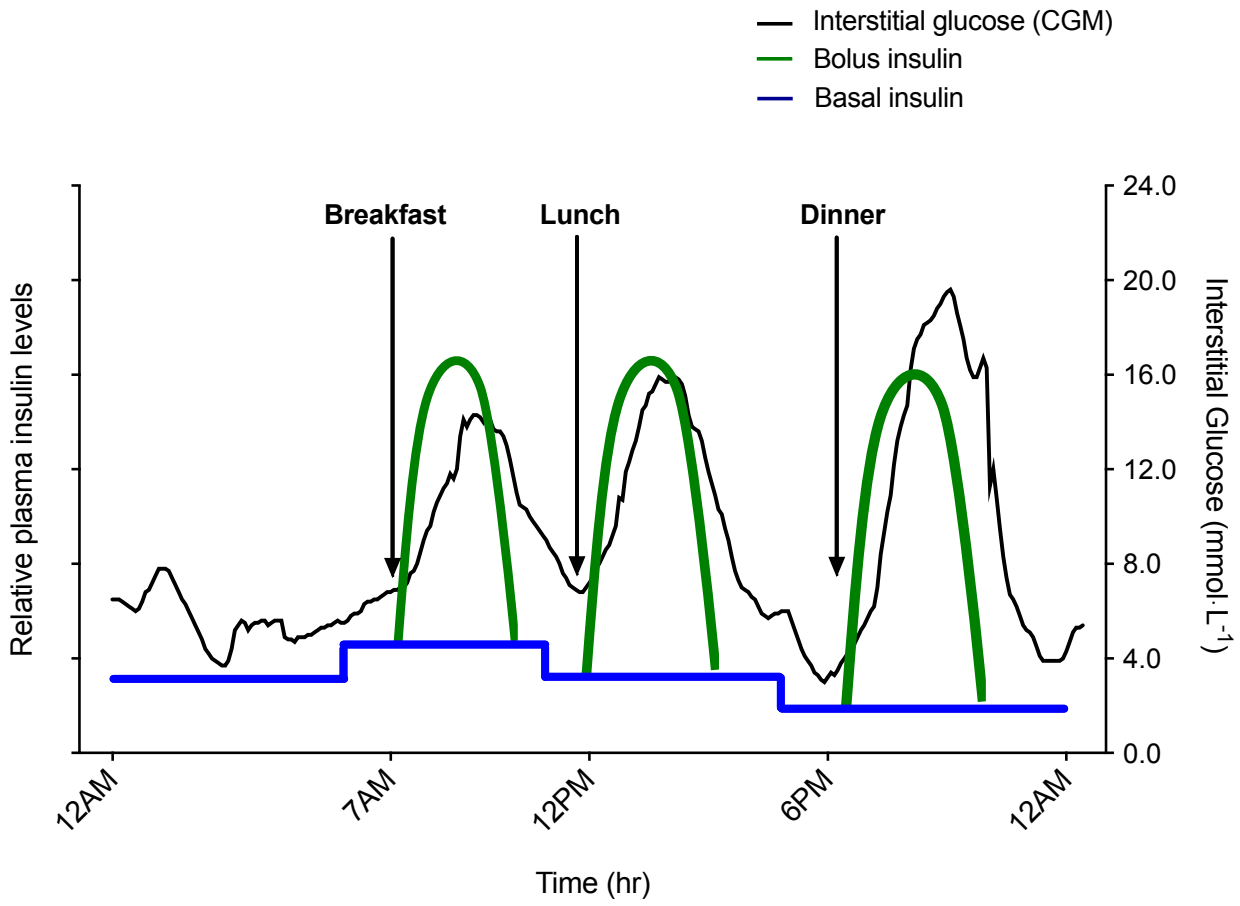


Figure 1.1: 'Basal-bolus insulin regimen' and interstitial glucose.

Standard 'basal-bolus insulin regimen' overlaid with interstitial glucose over 24 hours. Black represents the interstitial glucose data captured using a real-time continuous glucose monitor. Green represents the bolus insulin. Blue represents the basal insulin. Modified from Subramanian et al. (45).

Studies suggest that CSII versus MDI therapy is typically more effective for improving glucose variability and perhaps also HbA_{1c} levels (46-48). In some cases, CSII therapy has been more advantageous for patients with initial poor glycemic control (49, 50), while other studies found significant improvements with the transition from MDI to CSII therapy in well-controlled patients with type 1 diabetes (47, 51). In general, CSII treatment provides an efficient and more flexible means of delivering insulin and allows for more immediate basal insulin rate adjustments relative to MDI (52). Since a growing percentage of the type 1 diabetes population are transitioning to insulin pump therapy (53, 54), CSII will likely be the primary management strategy in the future for patients living with type 1 diabetes. As such, this thesis is limited to exercise studies on patients with type 1 diabetes that are using CSII therapy.

1.4 Physical activity and exercise

1.4.1 General exercise training adaptations

Habitual moderate-to-vigorous intensity aerobic training generally causes increases in overall heart mass and volume (26). More specifically, aerobic training leads to central and peripheral cardiovascular adaptations in a dose-dependent manner. Some of these central adaptations include improvements in stroke volume, cardiac output, blood volume, increases in end-diastolic volume, and greater oxygen extraction (55). Peripheral adaptations can include enhanced muscle blood flow and vasculature, and improved mitochondrial function and enzymatic activity. During exercise, blood flow is increased in the cardiovascular system to increase the delivery of oxygen and nutrients to meet the demands of the working muscles, and to remove carbon dioxide. Aerobic training also increases glucose transporter 4 (GLUT-4) content and improves glucose uptake into the skeletal muscles (56, 57).

Maximal intensity activities, commonly referred to as 'anaerobic', more fully engage all of the motor units especially the fast-twitch oxidative and glycolytic muscle fibres for very short bursts (10 seconds or less) and therefore, almost exclusively rely on energy from ATP and PCr in the muscles (26). Anaerobic training is very demanding on the human body and requires maximal or near-maximal effort which is not tolerated well by non-athletic individuals and therefore is less frequently undertaken when compared to aerobic training (12). With intermittent high intensity training, however, the bursts can vary from 10 seconds to three minutes and are interspersed with lower-intensity or rest periods in between. The difference with intermittent high intensity training is that in addition to the aerobic training benefits, there is added stress to the glycolytic system in the muscle and an improvement in the removal of lactate accumulation in skeletal muscles (12).

Resistance training includes activities that are progressive manipulations of volume, intensity, and frequency against a resistive force (e.g. free weights, weight machines, bodyweight, or resistance bands) (13). Moderate-to-vigorous intensity resistance training has been shown to cause muscle hypertrophy, increased muscle power, endurance, balance, agility and coordination (58). Based on the American College of Sports Medicine (ACSM) position statement, resistance training improves muscular strength on average from 15% in trained individuals to an average of 40% in untrained individuals (59). Progressive resistance training increases fast-twitch muscle fibres, mitochondrial density, and cross-sectional area, but appears to cause little-to-no change in glycolytic enzyme activity (12). Overall, safely executed resistance training has been shown to also increase muscular strength (60) and improve glucose tolerance and insulin sensitivity (61).

1.4.2 Physical activity and exercise benefits in T1D

Regular physical activity not only improves a number of health outcomes in individuals living with type 1 diabetes, but it can also improve the overall wellbeing (62), quality of life (5), and life expectancy (63) in this patient population. Some of these established health benefits include an increased aerobic fitness (64), increased insulin sensitivity (4, 65), improved lipid profiles (66, 67), improved endothelial function (68, 69), and reductions in cardiovascular disease (70) and mortality (63). In addition, increased levels of physical activity have also been associated with reductions in diabetes complications such as neuropathy, nephropathy, and retinopathy (71). Physical activity can be performed safely and yield these described benefits for individuals living with type 1 diabetes, but often requires significant pre-planning and knowledge of the upcoming activity in order to minimize hypoglycemia risk (72). These improvements in health outcomes need to be recognized as important tools and motivational strategies for patients with type 1 diabetes to be regularly active.

1.4.3 Exercise guidelines in T1D

Current guidelines and position statements recommend that adults with type 1 diabetes accumulate 150 minutes of physical activity per week with no more than two days of rest in between and additionally incorporating resistance training 2-3 times per week (2, 13, 14). Performing vigorous-intensity exercises at least 75 minutes weekly, although shorter in duration, can still elicit similar improvements in cardiovascular and overall fitness (73, 74). Based on the International Society for Pediatric Diabetes (ISPAD) clinical guidelines, toddlers are recommended to accumulate 60-90 minutes of physical activity daily (75). For preschoolers the recommendations are 90-120 minutes of physical activity daily, and for children and adolescents, the guidelines suggest at least 60 minutes of daily physical activity (75). Exercise guidelines and

position statements are intended to promote physical activity, but may still need to be customized to patients' individual needs. Interestingly, research has found that many children with type 1 diabetes are not adhering to clinical guidelines and in fact are participating in less than the recommended daily physical activity (76) and adults were also found to engage in fewer minutes of moderate-to-vigorous physical activity compared to individuals without type 1 diabetes (77).

Although exercise guidelines and position statements for individuals with type 1 diabetes exist (2, 13, 14, 78), a greater focus needs to be placed on determining what specific factors are contributing to this lack of activity. Brazeau et al. (77) suggest that the highest ranked barriers to physical activity in individuals with type 1 diabetes are a fear of severe hypoglycemia, loss of diabetes control, work schedule and low fitness levels. The use of CGM technology may help decrease the fear associated with hypoglycemia for individuals with type 1 diabetes as patients will be able to respond to glucose fluctuations sooner, before hypoglycemia ensues (79). In order to further reduce the burden or eliminate some of these barriers, more effective strategies around glycemic management during and post-exercise are required.

1.5 Metabolic responses to exercise in T1D

1.5.1 Glucose homeostasis during exercise in T1D

Dysglycemia associated with physical activity and exercise is caused by a number of factors including the timing, type, duration, and intensity of exercise. Blood glucose responses to physical activity and exercise are also impacted by prior hypoglycemia (80), starting glucose levels (81), and circulating insulin levels (82).

Aerobic activities tend to cause blood glucose levels to drop, primarily due to the body's inability to lower circulating insulin concentrations at exercise onset (82). In fact, a few studies have even shown insulin concentrations rise at the beginning of exercise and this is possibly

attributed to an increase in blood flow and subcutaneous insulin absorption (83, 84). Without additional carbohydrate supplementation before, during, or after exercise, hypoglycemia is a common occurrence with aerobic exercise. In type 1 diabetes, research suggests that impaired glucose counterregulation may be influencing the body's ability to attenuate the drop in glycemia during aerobic exercise (85). However, vigorous-to-maximal intensity activities generally shift fuel utilization from fat to carbohydrates (86). These higher-intensity activities also have an opposite effect on glycemia compared to aerobic activities and attenuate the drop in blood glucose level or cause blood glucose level to rise (87). This increase in blood glucose level during vigorous-to-maximal intensity bursts may be associated with a rise in counterregulatory and metabolic hormones (i.e. catecholamines, cortisol, growth hormone, etc.) restricting glucose disposal (88).

1.6 Hypoglycemia in T1D

For years, the primary research focus for patients living with type 1 diabetes has been on reducing the burden and incidence of hypoglycemia, a term often described as the limiting factor in glycemic control in patients using CSII therapy (89). In the past, the exact glycemic threshold for hypoglycemia occurrence has been argued, but the American Diabetes Association (ADA) workgroup determined that SMBG level of ≤ 3.9 mmol/L (≤ 70 mg/dL) is when individuals with type 1 diabetes often experience impaired cognition with hypoglycemia and this is the threshold for activating glucose counterregulation in patients without type 1 diabetes (90).

1.6.1 Glucose counterregulation in T1D

For individuals living with type 1 diabetes, the maintenance of euglycemia is often compromised with recurrent and sometimes frequent episodes of hypoglycemia. Exercise itself is a major contributor to hypoglycemia and it can also be a trigger for recurrent hypoglycemia over

the next 24 hours (16). Hypoglycemia symptoms are commonly divided into two categories: 1) neuroglycopenic and 2) neurogenic. Neuroglycopenic symptoms refer to impairments in cognition and behaviour and neurogenic symptoms refer to sweating, hunger, tremors and anxiety. In addition, patients with type 1 diabetes that experience repeated episodes of hypoglycemia can also become less symptomatic and develop decreased awareness of low blood glucose levels, termed hypoglycemia unawareness (91).

Hypoglycemia may be better described as *iatrogenic* hypoglycemia because it often occurs as a result of an accidental (i.e. unintentional) interplay between excess insulin and compromised physiological and behavioural defenses against decreasing glycemia (91). Episodes of symptomatic hypoglycemia for this population occur on average two times per week (92) and one in six experience at least one severe hypoglycemia episode per year (93). Three common defects contribute to the increased frequency of hypoglycemia in type 1 diabetes. These include: 1) the loss of β-cell function leading to the reliance of exogenous insulin therapy; 2) impaired counterregulation particularly with an abnormal glucagon response; and 3) reduced autonomic nervous system responses that often occur by 10 years of disease duration (94, 95). More specifically, research has established that in patients living with type 1 diabetes, the physiological defences against hypoglycemia including decreases in insulin and increases in glucagon are lost and increases in epinephrine are often attenuated (96-98) (Table 1.1). Without proper defence mechanisms against hypoglycemia, patients with type 1 diabetes are at a greater risk for developing severe hypoglycemia that can lead to a coma or ultimately death, if left untreated (99).

	Individuals *without* type 1 diabetes	Individuals *with* Type 1 diabetes
Pancreas	↓ insulin	Lost in T1D
Liver	↑ glucagon	Attenuated/lost in T1D
Kidneys	↑ epinephrine	Attenuated in T1D
Brain	↑ neurogenic symptoms	Attenuated in T1D

Table 1.1: Defences against hypoglycemia.

Physiological and behaviour defences against hypoglycemia in patients without and with type 1 diabetes. Modified from Cryer PE. The Barrier of Hypoglycemia in Diabetes. *Diabetes*, 2008, 57:12 (92).

1.6.2 Hypoglycemia unawareness in T1D

Geddes et al. (100) found that hypoglycemia unawareness leads to a six-fold increase in the likelihood of developing iatrogenic hypoglycemia. This increase in hypoglycemia unawareness is associated with the attenuation in epinephrine secretion that causes defective glucose counterregulation in patients with type 1 diabetes (92). The attenuation of epinephrine has been linked to a concept known as 'hypoglycemia-associated autonomic failure' (HAAF) that is associated with the following three factors: 1) recent (antecedent) hypoglycemia (98, 101); 2) prior exercise (102); or 3) sleep (103). Hypoglycaemia, exercise and sleep have all been shown to blunt the counterregulatory hormone response to subsequent hypoglycaemia. More specifically during sleep, Banaerer et al. (103) demonstrated that patients with type 1 diabetes were substantially less likely to be awakened by hypoglycemia due to reduced sympathoadrenal responses to hypoglycemia.

Interestingly, studies have reported that in most patients with type 1 diabetes, hypoglycemia unawareness is reversible with as little as a 2-3 week intervention of strict diabetes monitoring and avoidance of hypoglycemia (104, 105). Even in adults with long-standing type 1

diabetes (mean duration ~35 years), the HypoCOMPaSS trial showed recovery of hypoglycemia awareness with a 24-week intervention using an educational tool aimed at avoidance of hypoglycemia without worsening of overall glycemic control (106). Given the high incidence of hypoglycemia in type 1 diabetes, the use of rtCGM technology is on the rise since these systems can alert the patients that glucose levels are in, or are approaching, the hypoglycemic range (see below).

1.6.3 Exercise-related hypoglycemia in T1D

Regular physical activity and exercise increase the risk of severe hypoglycemia (107) and contribute to greater hypoglycemia risk following activity, for upwards of 24 hours in recovery (16, 108). A number of studies have found that 45 minutes of continuous steady state moderate intensity aerobic exercise in the late afternoon increases the risk of overnight (nocturnal) hypoglycemia for youth living with type 1 diabetes (81, 109, 110). Yardley et al. (111) were the first to suggest that performing resistance exercise before aerobic exercise in trained adults living with type 1 diabetes could lead to a smaller decrease in glycemia during exercise, but more importantly, may decrease the severity of potential nocturnal hypoglycemia. Since many individuals living with type 1 diabetes avoid physical activity due to a fear of hypoglycemia (112, 113), a number of novel strategies to promote exercise and help to reduce the fear of hypoglycemia will be discussed throughout this dissertation.

1.7 Glycemic management strategies during exercise in T1D

As previously discussed, regular physical activity and exercise can improve a number of health outcomes in a dose-dependent manner for individuals living with type 1 diabetes. However, physical activity and exercise can also lead to large fluctuations in glycemia during activity. Therefore, one of the biggest challenges is managing optimal glycemic control,

specifically around exercise. There are a number of strategies that can help reduce these glycemic disturbances associated with exercise; however, no one strategy has proven to be entirely effective. Some of the most common strategies discussed in the literature include 1) basal insulin adjustments, 2) bolus insulin adjustments, 3) carbohydrate feeding, and 4) a combination of these strategies. These strategies are discussed in detail below. In this section, short duration generally refers to exercise < 40 minutes in length whereas more prolonged refers to activity that is > 40 minutes in duration.

1.7.1 Basal insulin strategies

Basal insulin adjustments vary slightly for individuals using MDI versus CSII treatment. For individuals using MDI, basal insulin adjustments can only be made when long-acting insulin is administered, often in the early morning or before bedtime. For individuals using CSII therapy; however, there is greater flexibility around the timing of basal insulin adjustments. Since basal insulin is infused in a small dose over 24 hours, the adjustments can be made any time of the day.

Specifically in response to exercise, basal insulin adjustments can be made at the start of exercise, or several hours in advance of the activity. For patients using CSII, a basal-bolus reduction combination can be implemented in advance of exercise. Depending on the timing of exercise relative to meal ingestion, individuals can decide whether it is appropriate to adjust basal insulin, bolus insulin, or both. If individuals are exercising shortly after meal consumption (in the postprandial state), adjustments to bolus insulin can be made. Patients exercising in the post-absorptive state (often > three hours post-meal) often benefit from basal insulin adjustments because there is sufficient time to reduce circulating insulin levels (Figure 1.2).

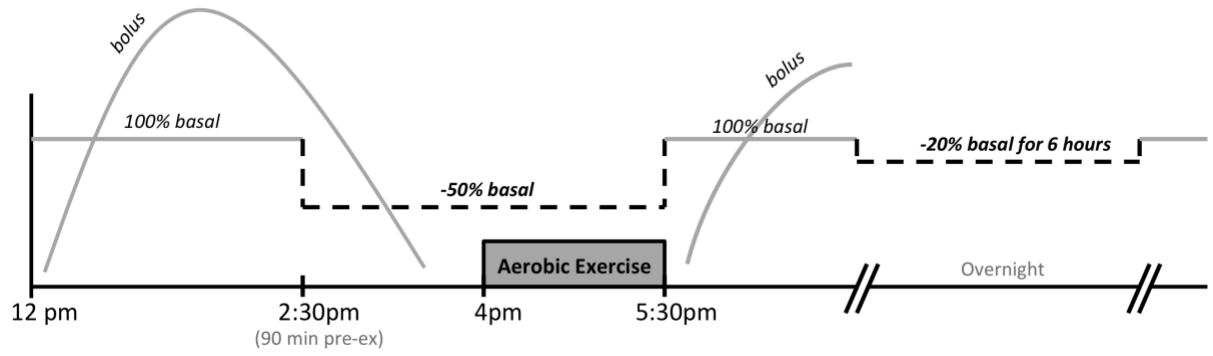


Figure 1.2: Basal rate reduction (BRR) strategies during and post-exercise.

Basal rate reductions (BRR) should made ~90 minutes before exercise and last until the end of exercise. Post-exercise, ~20% BRR are recommended at bedtime for six hours overnight to help combat nocturnal hypoglycemia. Published by Zaharieva & Riddell, Can J Diabetes 2017 (114). Reproduced with permission from the publisher.

When physical activity and exercise is spontaneous or unplanned, basal rate reductions (BRR) can only be made at the start of activity and/or in recovery. For shorter duration (< 40 minutes) aerobic exercise, studies have shown that BRR at exercise onset may decrease the likelihood of hypoglycemia during exercise (83, 115), but is still associated with a large drop in glycemia (116). In a more recent study, even with an 80% BRR set 40 minutes pre-exercise, hypoglycemia could not be reduced (117). Ideally, BRR should be set at least 60-90 minutes before the onset of exercise, in order for insulin concentrations to have time to drop in the circulation (13, 117). However, this type of BRR requires significant pre-planning and may not be feasible for many children or adolescents that more commonly engage in unplanned activity. Further research is required to understand whether this recommendation applies to all patients living with type 1 diabetes and whether this strategy is still effective with more prolonged aerobic activity. One of the concerns about reducing basal insulin well in advance of the exercise

is that blood glucose level may begin to rise before the exercise onset (118). Also, reducing basal insulin too far in advance of exercise may ultimately contribute to post-exercise rebound hyperglycemia.

For resistance and circuit-based exercise, blood glucose concentrations tend to remain more stable than during aerobic exercise. Therefore, BRR for this type of exercise may not need to be as aggressive as those recommended for aerobic exercise. At rest, the time that it takes for insulin levels to drop in the circulation remains the same (119), therefore, reducing basal insulin would still be recommended 60-90 minutes before resistance and circuit-based exercise. In a study by Yardley et al. (120), patients using MDI therapy reduced basal insulin by 10% on exercise days and patients using CSII performed a 50% BRR 1 hour before exercise until the end of exercise and both groups found that blood glucose levels dropped more rapidly with aerobic compared to resistance exercise. However, these BRR strategies with resistance exercise may not be enough to protect from late-onset nocturnal hypoglycemia (120). Therefore, in addition to reducing basal insulin, mealtime bolus insulin reductions may also be required to better protect against hypoglycemia in recovery (see section 1.7.2 bolus insulin strategies).

It is also important to consider BRR strategies that can protect against exercise-associated hypoglycemia in recovery and overnight. For example, since exercise increases insulin sensitivity (4) and studies have shown that this increase can last for up to 24 hours post-exercise (108), reducing basal insulin by 20% for 6 hours overnight can help protect against post-exercise nocturnal hypoglycemia (13). Table 1.2 represents various BRR strategies that individuals using CSII therapy may want to consider for both short duration and more prolonged activities, as well as post-exercise.

Table 1.2: Basal insulin adjustment strategies for CSII

	Exercise (< 40 Minutes)	**Exercise** (> 40 Minutes)	**After Exercise**
AEROBIC Light-to-moderate intensity continuous exercise	50% BRR, set 60-90 min pre-exercise) or Pump suspension at exercise onset*	50-80% BRR set 60-90 min pre-exercise) or Pump suspension at exercise onset*	20% BRR overnight from bedtime lasting 6 h
RESISTANCE Moderate-to-vigorous intensity	No reduction typically performed	50% BRR, set 60-90 min pre-exercise)	20% BRR overnight from bedtime for 6 h
BRIEF INTENSE ANAEROBIC Maximal intensity	Not applicable: Exercise typically lasts seconds to minutes		No reduction typically performed †
MIXED Low-to-moderate with intermittent moderate-to-vigorous intensity bursts	Pump suspension at exercise onset*	50% BRR, set 60-90 min pre-exercise) or Pump suspension at exercise onset*	20% BRR overnight from bedtime for 6 h

Notes: Suggested starting points for basal rate reductions (BRR) for various types and durations of exercise (not all recommendations have been formally tested). BRR are typically made when the exercise is in the fasted state or several (three or more hours) after a meal. For activities that occur soon after meals (within three hours), bolus insulin should be adjusted (see table 1.2 above). Knowing the type of activity that is being performed will guide the basal rate adjustments, as described above. This summary table is based on studies conducted in type 1 diabetes (83, 116, 117, 120-122). * = Carbohydrate may be required since insulin levels may not drop fast enough during the activity. † = Post-exercise hyperglycemia should be treated with a bolus insulin correction rather than a basal rate change. Adapted from Zaharieva & Riddell, Can J Diabetes 2017 (114).

1.7.2 Bolus insulin strategies

Another strategy to reduce the likelihood of hypoglycemia during exercise is to reduce bolus insulin, often relative to mealtime. Generally, the best time to perform bolus adjustments would be when aerobic exercise is performed within 1-3 hours of a meal (114, 123). In order to effectively execute this strategy, knowledge about the timing, duration, and intensity of the activity and also some advanced planning are required. Moreover, in situations where physical activity is going to be performed more than three hours following a mealtime bolus, then bolus reductions are often unnecessary (Figure 1.3).

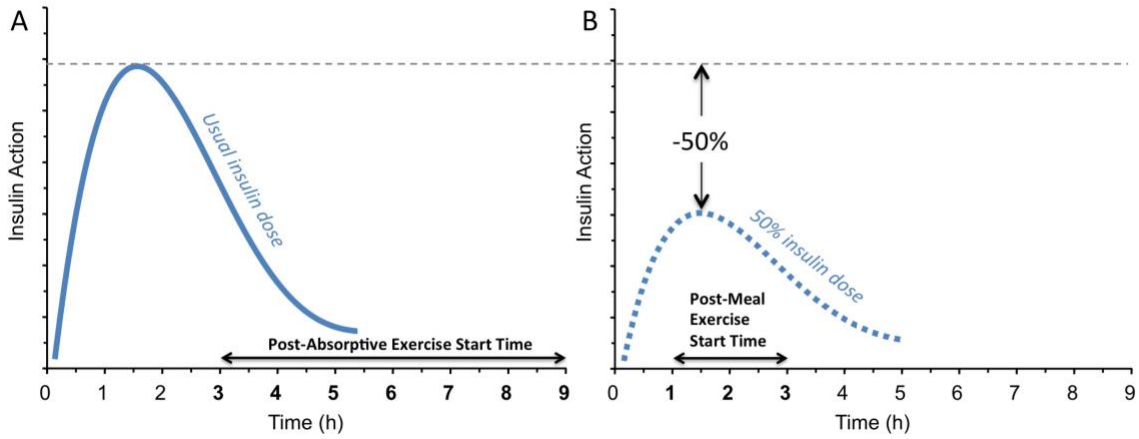


Figure 1.3: Bolus insulin adjustment strategies for exercise.

Strategies of bolus adjustments for exercise relative to meal ingestion. A, exercise occurring three or more hours post-meal, generally does not require a bolus adjustment. B, for exercise taking place 1-3 hours post-meal, generally, a 50% reduction in bolus insulin is required with the meal before exercise. These recommendations are applicable for aerobic exercise lasting > 40 minutes. Published by Zaharieva & Riddell, Can J Diabetes 2017 (114), reproduced with permission from the publisher.

When deciding on the appropriate bolus insulin adjustment necessary to maintain blood glucose concentration, the type, duration, and intensity of exercise being performed will impact the amplitude of change. For example, a larger mealtime bolus reduction is required with prolonged light-to-moderate intensity aerobic activities compared to intermittent high intensity exercise (13). This occurs because muscle glucose uptake exceeds glucose production by the liver and insulin levels do not drop during aerobic exercise (16). Intermittent high intensity exercise increases counterregulatory hormones (124, 125) and lactate concentration that stimulates gluconeogenesis and often cause increases in glucose concentration during and post-exercise (125). Therefore, intermittent high intensity exercise is generally associated with lower hypoglycemia risk during and within two hours post-exercise, and typically requires a smaller bolus insulin reduction.

In general, short duration aerobic exercises (< 40 minutes) require a 25-50% meal bolus reduction, whereas more prolonged aerobic activities (> 40 minutes) require a 50-75% bolus reduction at mealtime (123, 126, 127). Ultimately, a more aggressive reduction in bolus insulin and a delay in exercise start time can increase the risk of elevated blood glucose levels before exercise onset, but as long as some insulin is administered, ketone production does not appear to be significantly impacted (126, 128). Table 1.3 represents various bolus adjustment strategies relative to the intensity and duration of exercise and are based on previously published studies.

Table 1.3: Bolus insulin adjustments for post-prandial exercise

	Meal Before Exercise		Meal After Exercise
	Exercise (< 40 Minutes)	**Exercise** (> 40 Minutes)	
AEROBIC Continuous steady state light-to-moderate intensity exercise	25-50% bolus reduction	50-75% bolus reduction	25-50% bolus reduction
RESISTANCE Moderate-to-vigorous intensity	No reduction typically performed	25-50% bolus reduction	No change in bolus
BRIEF INTENSE ANAEROBIC Maximal intensity	Not applicable: Exercise typically lasts only a few minutes		Small (~50%) bolus correction if hyperglycemic*
MIXED Low-to-moderate with intermittent moderate-to-vigorous intensity bursts	~ 25% bolus reduction	~ 50% bolus reduction	25-50% bolus reduction

Notes: Suggested starting points for bolus insulin reductions for various types and durations of exercise (not all recommendations have been formally tested). These suggestions are for rapid-acting insulin only. Bolus insulin adjustments are typically made when the exercise is performed within 1-3 hours following a meal. Knowing the type of activity that is being performed will guide the bolus insulin adjustments, as described above. This summary table is based on studies conducted on patients with type 1 diabetes using bolus adjustments (122, 123, 126, 129-132). * = Requires continued monitoring to help protect against post-exercise hypoglycemia, particularly overnight. Adapted from Zaharieva & Riddell, Can J Diabetes 2017 (114).

Research studies often focus on bolus insulin adjustment strategies for aerobic exercise since this particular type of activity increases the risk of hypoglycemia. Activities that are mixed in nature, which includes light-to-moderate intensity activities that are interspersed with intermittent, moderate-to-vigorous and vigorous-to-maximal intensity bursts, have a lower risk of hypoglycemia and therefore, may require a less aggressive insulin dose reduction with the meal preceding exercise (88). For moderate-intensity resistance exercise performed under fasting conditions in the morning, Turner et al. (132) found that the delivery of an individualized dose of rapid-acting insulin, based on the patient's own insulin sensitivity index (i.e. a 50% correction factor), could reduce the likelihood of post-exercise hyperglycemia. This study is a good starting point to help reduce hyperglycemia following morning exercise, but further investigations are required for the delivery of rapid-acting insulin following resistance exercise.

1.7.3 Carbohydrate feeding strategies

Carbohydrate ingestion is often used as a treatment for hypoglycemia, but for the prevention of hypoglycemia during exercise, the exact timing and amount of carbohydrates remains unclear. In terms of prevention strategies for exercise-associated hypoglycemia, carbohydrate feeding often requires less pre-planning compared to basal and bolus adjustments and therefore may be more common than the two previously discussed strategies.

Carbohydrate feeding to prevent hypoglycemia does not only depend on the intensity and duration of exercise (13, 133), but can also change depending on circulating insulin concentration. Specifically, in underinsulinized or low insulin conditions, fewer grams of carbohydrates are needed to prevent hypoglycemia compared to overinsulinized or high insulin conditions (13). In many cases, it is more beneficial for individuals with type 1 diabetes to begin exercising with lower circulating insulin concentrations and therefore, reduce the amount of

carbohydrate supplementation needed pre-exercise. Although this strategy may not always be feasible or preferred, it is important to attempt exercising with lower insulin in the circulation or 'on-board', where applicable. Starting blood glucose levels pre-exercise are also a strong predictor for the amount of carbohydrate ingestion required to prevent hypoglycemia during exercise (81).

1.7.4 Carbohydrate and insulin strategies combined

Grimm et al. (134) showed that proper supplementation of carbohydrates or carbohydrate feeding and insulin adjustments for exercise are more effective at reducing hypoglycemia compared to insulin reduction strategies alone or no changes to insulin at all. This is likely because carbohydrate supplementation is easier to apply and requires less pre-planning compared to reducing basal insulin levels well before the start of exercise. When combining carbohydrate feeding and insulin adjustments, the recommendations also can change depending on the duration and type of exercise being performed.

Taking into consideration starting blood glucose concentration at exercise onset and the approximate amount of circulating insulin, we created a schematic called the "Zone-Based Approach for Exercise" (Figure 1.4). This schematic shows that higher levels of insulin in the circulation at exercise start will require greater carbohydrate supplementation compared to low circulating insulin during exercise in order to prevent hypoglycemia (134).

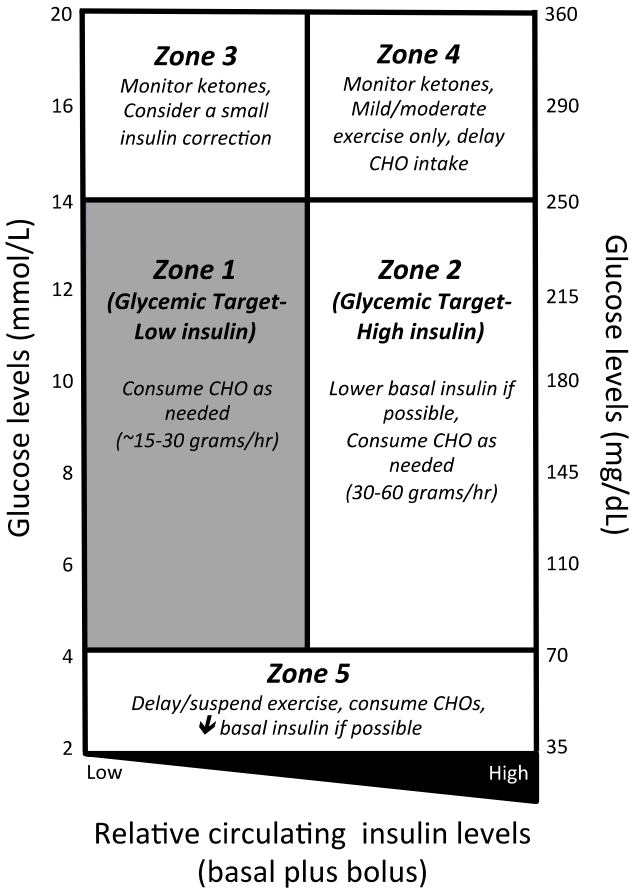


Figure 1.4: 'The Zone-Based Approach for Exercise'.

Carbohydrate and insulin strategies for aerobic exercise based on starting blood glucose and relative circulating insulin levels. *Zone 1* is suitable for prolonged aerobic exercise and for anaerobic and mixed exercise. *Zone 2* is suitable for prolonged aerobic exercise but typically requires some carbohydrate feeding and/or basal insulin reductions if possible (patients using CSII only). Anaerobic and mixed exercise can be initiated. *Zone 3* requires ketone monitoring before exercise and insulin administration if ketones are elevated above trace level. Exercise should be avoided until control is re-established. *Zone 4* also requires ketone monitoring to confirm that ketones are low before start of moderate-intensity aerobic exercise. *Zone 5* requires carbohydrate feeding before the start of exercise (~15–30 g, depending on the amount of insulin in the circulation). In all of these zones, close glucose monitoring is advised. CHO, carbohydrate.

Published by Zaharieva & Riddell, Can J Diabetes 2017 (114). Reproduced with permission from the publisher.

Referring to Figure 1.4, Zone 1 occurs when the blood glucose level is in target range with low circulating insulin levels. This zone does not require significant carbohydrate feeding (< 0.5 grams per kilogram per hour of exercise) during aerobic exercise to maintain glycemia in target range. Zone 1 usually requires the reduction of basal insulin before exercise and limited carbohydrate consumption pre-exercise. Adolfsson et al. (135) suggests for prolonged aerobic exercise, higher carbohydrate intake may be preferred for performance reasons (up to 75 grams per hour) and in this case, insulin is typically required. If insulin is administered with high carbohydrate feeding, individuals will now be in Zone 2.

Zone 2 is when blood glucose level is in target range with relatively high insulin levels in circulation. At the start of aerobic exercise, this is a common situation for patients who have not pre-planned by lowering basal insulin in advance of the activity. Because of the relatively high circulating insulin levels, blood glucose concentrations can be expected to drop shortly after exercise is initiated, and hypoglycemia risk will be high unless carbohydrates are consumed. By increasing carbohydrate intake [up to ~ 60 grams/hour (136)] to offset the increase in insulin sensitivity while also lowering basal insulin levels, blood glucose levels can still be maintained in a reasonable range during exercise.

Zone 3 is when pre-exercise blood glucose level is elevated but patients have relatively low circulating insulin levels. In this situation, a small bolus insulin correction (i.e. 30%–50% of correction dose) may be required to treat hyperglycemia and limit ketone production before exercise.

Zone 4 is when blood glucose level is elevated and patients have high circulating insulin. This situation may be caused by high carbohydrate intake pre-exercise relative to the insulin

dosage or from competition stress. In this setting, patients can begin mild to moderate aerobic exercise (~40%–60% maximal aerobic capacity), since blood glucose will likely drop during exercise. Patients receiving a CSII therapy have an advantage over those receiving MDI therapy with this zone-based approach, since the former group can observe the level of 'on-board' or 'active' bolus insulin on the insulin pump device before starting exercise and can lower or suspend insulin delivery if blood glucose levels trend toward hypoglycemia during the activity.

Zone 5 is when patients are already experiencing hypoglycemia ([blood glucose] < 3.9 mmol/L) and often occurs if the insulin dose was miscalculated and exceeded the necessary amount for the carbohydrates consumed at the meal or snack before exercise. In this situation, exercise should be delayed until carbohydrate ingestion occurs (~20–30 grams) and/or basal insulin level is reduced (this applied to patients receiving CSII therapy only) in order to increase blood glucose level.

1.7.5 Blood glucose estimations

As we know, the type, intensity and duration of exercise can impact blood glucose concentration differently (13). Therefore, it is essential for patients with type 1 diabetes to know their blood glucose level, particularly before engaging in physical activity or exercise. Cox et al. (137) were the first to describe that estimating blood glucose fluctuations is not a fixed phenomenon, but varies across individuals. As such, throughout this thesis dissertation, we compared estimated versus measured blood glucose level, particularly during exercise. We blinded our participants to their measured blood glucose values and they were directed to estimate their glucose level at each SMBG measurement during exercise. If hypoglycemia occurred during exercise, the measured blood glucose value was immediately revealed to the participant and the exercise was suspended.

1.8 Technological advancements in T1D

1.8.1 Continuous and Flash Glucose Monitoring

Continuous glucose monitoring (CGM) devices often consist of a glucose sensor that is placed subcutaneous and is connected to a transmitter that can measure interstitial glucose levels every few minutes for approximately 7-10 days (41). These devices can report glucose values either in 'real-time' or they are 'blinded' and report data retrospectively. These 'blinded' devices are often called professional glucose-monitoring devices. Similar to the CGM, a flash glucose-monitoring (FGM) device requires a remote 'reader' to be scanned over the monitor in order to report a glucose reading. Eversense® recently launched the first ever patented polymer technology glucose sensor that is implanted by a trained professional (138). This device uses an external transmitter that sits on top of the skin and continually measures interstitial glucose levels for up to 90 days. Table 1.4 outlines all of the current personal and professional glucose monitoring devices on the market to date.

Pickup et al. (139) showed that in individuals with type 1 diabetes, CGM devices improve overall glycemic control compared to SMBG. Although frequent SMBG is an important tool for diabetes management and has been shown to lower HbA_{1c} levels (140, 141), it cannot predict the impending rise and fall in glycemia or provide alerts which CGM devices are capable of doing (142). More importantly, with the use of CGM, studies have shown that following afternoon exercise, there is an increased risk of nocturnal hypoglycemia (116, 143) and this can last up to 24 hours post-exercise (144). As previously discussed, a number of studies have contributed to the recent recommendations of reducing basal insulin overnight to better protect against post-exercise nocturnal hypoglycemia (121, 122, 145).

Glucose-monitoring devices are robust research tools and are evolving into the standard of care for type 1 diabetes management (146). These devices should be used alongside HbA_{1c} measures to improve glycemic control (41). As previously mentioned, GV and GMI are two measures that provide a more personalized profile of diabetes management using CGM. A mathematical calculation that measures the amplitude and timing of glucose excursions using CGM data is referred to as GV (42). In order to optimize glucose concentrations, there must be a reduction in GV and in turn, fewer episodes of hypoglycemia. As an additional measure of diabetes control, GMI can be calculated using CGM values from as little as 10-14 days to determine mean glucose and estimate HbA_{1c} levels (43, 147).

However, a primary concern regarding CGM and/or FGM use for patients with diabetes is that insurance companies and governments in most countries around the world do not offer cost reimbursement for these devices (148). Now that this technology is emerging as the standard of care for diabetes management (146), cost reduction and/or increased coverage nationwide is necessary.

	PERSONAL INTERSTITIAL GLUCOSE-MONITORING DEVICES							PROFESSIONAL INTERSTITIAL GLUCOSE-MONITORING DEVICES		
Model	Dexcom G4® or G5®	Dexcom G6®	Medtronic Guardian™ Link	Medtronic Guardian™ Link 3	Medtronic Guardian Connect	Abbott FreeStyle Libre	Eversense® Senseonics™	Dexcom G4® Platinum	Medtronic iPro™ 2	Freestyle Libre Pro
Receiver	Stand-alone receiver or smart phone	Stand-alone receiver or smart phone	Enlite sensor 630G insulin pump	Guardian sensor 3 670G insulin pump	Compatible smart phone	Stand-alone "reader"	Smart phone	Stand-alone receiver	Enlite sensor	Stand-alone "reader"
Sensor Life	7 days	10 days	7 days	7 days	7 days	14 days	90 days	7 days	7 days	14 days
Warm-up Period	2 hours	2 hours	2 hours	2 hours	2 hours	1 hour	24 hours	2 hours	2 hours	1 hour
Calibration	At least every 12 hours	Factory calibrated	At least every 12 hours	At least every 12 hours	At least every 12 hours	Factory calibrated	2x daily	At least every 12 hours	At least every 12 hours	Factory calibrated
Receiver Range	7m	7m	1.8m	1.8m	7m	Scan reader (1.5" from sensor)	7.6m	7m	N/A	Scan reader (1.5" from sensor)

Table 1.4: Personal and professional glucose-monitoring devices.
A comparison and description of different personal and professional (blinded) interstitial glucose-monitoring devices. Information includes the model, type of receiver, sensor life, warm-up period, calibration, and receiver range. Data retrieved from the following sources: (7, 149).

1.8.2 Closed-loop systems

Closed-loop insulin delivery systems, sometimes referred to as artificial pancreas systems, combine insulin pump therapy and rtCGM with a control algorithm that automates insulin delivery depending on changes in sensor glucose levels (150). The rtCGM and control algorithm communicate with one another in order to compute the appropriate amount of insulin and/or glucagon that needs to be delivered every few minutes to the patient in order to maintain near-physiological glucose ranges (151). Closed-loop systems can refer to single-hormone (insulin only) or dual-hormone (insulin and glucagon) systems that automate the delivery of one, or both hormones in a glucose-responsive fashion. This advanced technology communicates directly to an insulin pump or to a separate smartphone device. A number of earlier randomized control trials showed that closed-loop systems significantly increased the percent time in target glucose range and also reduced the time spent in hypoglycaemia (152-154). Recently, closed-loop studies have also showed improvements in overall glycemic control and decreases in HbA_{1c} with safe, in-home studies lasting upwards of 3-6 months (155, 156). These studies were the foundation around the clinical importance of closed-loop systems in type 1 diabetes management.

Because hypoglycemia is a prominent concern in patients living with type 1 diabetes, closed-loop studies focus on increasing time in range particularly overnight since during this time period, fewer variables (i.e. food, stress, exercise) impact glycemia. A number of studies showed improvements in glycemic management and reductions in nocturnal hypoglycemia with closed-loop systems, even with physical activity and exercise (157-160). Jacobs et al. (161) showed that with a dual-hormone closed-loop system that adjusted insulin and glucagon at exercise onset, hypoglycemia was significantly reduced compared to no adjustments.

In addition to fewer hypoglycemia events and overall improvements in HbA_{1c}, the goal of closed-loop systems is to remove some of the patient load and pre-planning often associated with diabetes management. Recently, Adams et al. (162) investigated the impact of a closed-loop trial on psychosocial and human factors and found that participants' management distress decreased, thereby showing that closed-loop systems provide promise for reducing the burden associated with diabetes control.

1.9 Challenges with technology

1.9.1 Challenges with CGM technology

Limitations in CGM technology are often related to a physiologic lag between sensor glucose and blood glucose concentration, estimated to range from a 7-8 minute delay in patients with type 1 diabetes in the fasting state (163). Physiologic delays in CGM can increase significantly with rapid changes in glycemia (7), such as during aerobic exercise and can differ depending on the CGM devices being used (164). The lag in sensor and blood glucose is often described in parts including (1) physiologic lag; (2) sensor reaction time; and (3) sensor signal processing time (7). Physiologic lag, sometimes referred to as equilibration time, is related to a time lag associated with the movement of glucose from the vascular to the interstitial fluid space in the subcutaneous adipose tissue (165). It takes time for the diffusion of glucose across capillary vessels and into the interstitial space (166). The sensor reaction time is the time it takes for glucose to diffuse into the sensor, which requires the collection and storage of data (167). This may also be related to delays in converting the voltage signal from the sensor to an estimate of blood glucose. And finally, sensor-processing time may lag because it incorporates a moving average filter to the data in order to smooth sensor glucose values (167).

With the use of technology, there is also a chance of user and/or measurement error in the devices themselves. The differences in CGM and blood glucose values may also be impacted by errors in the timing of CGM calibration or errors in the reference blood glucose measurement (167).

1.9.2 Challenges with closed-loop technology

Most of the challenges around closed-loop technology often occur in the daytime hours where factors such as the timing and type of food ingestion and/or exercise vary and can significantly impact glycemic control. Particularly challenging with meal ingestion and following insulin infusion is the delayed postprandial glucose response. To overcome these challenges, closed-loop systems in the present day are often referred to as 'hybrid closed-loop' systems because they are not all fully automated and some still require user input. For example, meal and/or exercise announcements are manually entered into the insulin pump (160). This user input allows the control algorithm to respond and make appropriate adjustments to insulin and/or glucagon before glycemic excursions occur. As previously discussed, depending on the intensity, type, and duration of exercise being performed, the energy utilization, glycemic responses, and ultimately insulin needs can vary as well. Therefore, closed-loop systems need to be able to assess the type of activity being performed in real-time (15) and the incorporation of wearable activity monitors has made this easier (168). Interestingly, Turksoy et al. (151) recently reported fewer hypoglycemia events during exercise with their control algorithm that requires no exercise announcements. However, in this study, glucose concentration still declined consistently during exercise and in recovery periods.

There is still some debate whether single or dual hormone closed-loop systems are more safe and effective for preventing hypoglycemia, improving time in range, and reducing glucose

variability in patients living with type 1 diabetes. Some additional challenges with the dual-hormone closed-loop system is the stability of glucagon once it has been reconstituted (150) and the potential side effects of chronic glucagon delivery that have yet to be assessed (169). More specifically, when glucagon is reconstituted in an aqueous solution, it is unstable and undergoes aggregation and rapid breakdown (170). Although glucagon is the primary treatment for emergency hypoglycemia because it works fast and effectively, following the reconstitution of the lyophilized powder, if kept in an aqueous solution over time, it begins to form firm gels that eventually can lead to a blockage in insulin pump infusion sites (171). As such, glucagon use in closed-loop systems remains a challenge and is currently limited to research studies with frequent replacements to prevent a blockage.

2.0 SUMMARY OF INTENT

2.1 Overall Research Objectives

The studies presented in this thesis examined the impact of different insulin strategies on blood glucose during and after exercise in individuals living with type 1 diabetes. These research projects also investigated the accuracy and impact of glucose monitoring devices during exercise as well as the impact of exercise on interstitial glucose concentration overnight. The overall purpose of this thesis dissertation was to elucidate optimal strategies to reduce the likelihood of hypoglycemia during exercise and in recovery.

2.2 Research Purpose

1) To examine the effect of suspending basal insulin at the onset of continuous steady state moderate intensity aerobic exercise versus circuit-based exercise. In addition, to investigate whether participants would be able to accurately estimate their blood glucose level during both types of exercise **(academic paper #1)**.
2) To determine the impact of suspending basal insulin (i.e. 'pump off') at exercise onset versus administering a 50% basal insulin reduction (i.e. 'pump on') during intermittent high intensity exercise. Also, to examine whether participants would be able to accurately estimate their blood glucose level during both conditions **(academic paper #2)**.
3) To investigate whether 80% or 50% basal insulin reduction set 90 minutes pre-exercise would attenuate the drop in blood glucose concentration compared to basal insulin suspension at the onset of continuous steady state moderate intensity aerobic exercise. Also, to investigate how reducing basal insulin 90 minutes pre-exercise would impact glycemic control following the meal post-exercise **(academic paper #3)**.
4) To assess the accuracy of newer rtCGM technology versus SMBG levels during and after continuous steady state moderate intensity aerobic exercise **(academic paper #4)**.

2.3 Research Hypotheses

1) Suspending basal insulin at the onset of aerobic exercise would lead to a greater drop in glycemia compared to circuit exercise. Participants would be able to accurately estimate their blood glucose level during both types of exercise.
2) Insulin 'pump off' at the onset of intermittent high intensity exercise would lead to a smaller drop in glycemia versus 'pump on' (at 50% of usual basal rate) during intermittent high intensity exercise and participants would be able to accurately estimate their blood glucose level during both conditions.
3) Reducing basal insulin 90 minutes before aerobic exercise would attenuate the drop in glycemia versus suspension of basal insulin at the onset of exercise in type 1 diabetes. Reducing basal insulin 90 minutes pre-exercise would also lead to greater blood glucose excursions during the meal post-exercise.
4) Real-time continuous glucose monitoring would underestimate the true drop in glycemia associated with aerobic exercise due to a time delay between blood and interstitial glucose level.

3.0 ACADEMIC PAPER 1

The effects of basal insulin suspension at the start of exercise on blood glucose levels during continuous vs. circuit-based exercise in individuals with type 1 diabetes on CSII.

Published in Diabetes Technology and Therapeutics, 2017

The effects of basal insulin suspension on blood glucose concentrations during continuous and circuit-based exercise in individuals with type 1 diabetes on CSII.

Short Title: Continuous versus Circuit Exercise on Blood Glucose

Dessi Zaharieva[1], Loren Yavelberg[1], Veronica Jamnik[1], Ali Cinar[2,3], and Michael Riddell[1]

[1] – Department of Kinesiology & Health Science, Faculty of Health, Muscle Health Research Centre and Physical Activity & Chronic Disease Unit, York University, Toronto, ON, Canada

[2] – Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, USA

[3] – Department of Chemical & Biological Engineering, Illinois Institute of Technology, Chicago, IL, USA

Correspondence to:

Dr. Michael Riddell, Ph.D.

Department of Kinesiology and Health Science

York University

4700 Keele Street,

Toronto, Ontario

M3J 1P3

Keywords: Hypoglycemia, Exercise, CSII, Basal Insulin, Blood Glucose

Abstract

Aim: To examine whether suspending basal insulin at the onset of exercise can reduce the likelihood of hypoglycemia during 40 minutes of continuous (CON) steady state moderate intensity exercise versus circuit-based (CIRC) exercise. Also, to examine whether blood glucose (BG) estimations are accurate during CON vs. CIRC exercise.

Methods: Twelve individuals (6 males, 6 females) with type 1 diabetes on insulin pump therapy were recruited for the study. All participants completed a maximal oxygen consumption (VO_2max) test and two 40-minute sessions (consisting of either a continuous treadmill walking/light jogging or circuit workout). Basal insulin was stopped at the onset of both exercise modalities and resumed to the regular rate immediately post-exercise.

Results: Relative VO_2 (47.5 ± 7.5 vs. 54.5 ± 13.5 $mL \cdot kg \cdot min^{-1}$, $P = 0.03$) and heart rate (122 ± 20 vs. 144 ± 20 beats per minute, $P = 0.003$) were lower with CON vs. CIRC exercise. A trial by time interaction ($P = 0.001$) shows significantly lower BG concentrations with CON compared to CIRC exercise. The overall drop in BG was greater in CON vs. CIRC exercise (delta -3.7 ± 1.5 vs. -1.3 ± 2.6 $mmol \cdot L^{-1}$). A group analysis indicated that participants frequently estimated their BG levels within 20% of the measured reference value with reasonable accuracy during both forms of exercise (71% vs. 63% with a mean bias of -0.1 ± 2.6 mmol/L [± 2 SD] vs. -0.1 ± 4.4 mmol/L for the CON versus CIRC conditions, respectively). Participants were able to estimate their BG levels more accurately during CON (r = 0.83) vs. CIRC exercise (r = 0.33) based on a regression analysis.

Conclusion: Therefore, even with basal insulin suspension and lower exercise intensity, CON results in a larger drop in BG level compared with CIRC exercise. These findings may have implications for single hormone-based artificial pancreas development for exercise.

Suspension of insulin infusion at the onset of CON exercise may not be sufficient to prevent hypoglycemia. While this study does not negate the importance of frequent capillary BG monitoring during exercise, it does suggest that if persons are knowledgeable about their pre-exercise BG level, they can exercise safely without the need for stopping to monitor over at least a 40-minute period of CON physical activity.

Introduction

Regular physical activity (PA) is recommended for improving insulin sensitivity, blood lipid profiles and for reducing the risk of cardiovascular disease for individuals with type 1 diabetes (T1D) (13). Aerobic exercise can increase the likelihood of hypoglycemia and may also lead to challenges in maintaining blood glucose (BG) control overall (172). Without insulin dose adjustments or carbohydrate intake, continuous steady state moderate intensity aerobic exercise (CON) typically leads to large reductions in BG level (81), whereas sprint-based exercise and intermittent high intensity circuit-based (CIRC) exercise either attenuates the decrease, or may even cause a small rise in BG level (124, 173, 174). While both CON and CIRC can lead to specific training adaptations, individuals with T1D would likely choose CIRC exercise for a variety of reasons, including enhanced fitness (175) without promoting nocturnal hypoglycemia (174).

Tsalikian and colleagues (176) demonstrated that the risk of developing exercise-associated hypoglycemia could be effectively reduced with the suspension of insulin infusion (i.e. pump suspend) in children on continuous subcutaneous insulin infusion (CSII) therapy. In contrast, Admon et al. (115) found that pump suspension did not attenuate the drop in glycemia compared to leaving the pump on with a reduced basal rate (i.e. 50%). In a more recent study, McAuley et al. (84) reported that a basal rate reduction of 50% performed 60 minutes prior to the start of exercise failed to cause a significant reduction in circulating insulin levels during exercise compared to baseline. In all of these studies, only one type of exercise was performed (i.e. CON). Therefore, further research is required on the impact of different types and intensities of exercise on BG levels.

Since exercise can increase the likelihood of glycemic disturbances in patients with T1D, it is important for frequent BG monitoring before, during, and after activity. A few studies have assessed the accuracy of estimating BG level versus measured BG level in individuals with T1D (137, 177); however, to our knowledge, no studies have assessed the accuracy of BG estimations specifically during exercise. In certain situations, capillary BG monitoring may be difficult during sport. As such, we need to better understand how exercise may impact the ability for patients to estimate their BG level.

The primary purpose of this study was to examine the effects of basal insulin suspension at the onset of two different forms of exercise (i.e. CON versus CIRC). The secondary purpose was to assess the accuracy of BG estimation when participants were provided with their measured BG value 10 minutes prior to the onset of exercise. Our hypothesis was that suspending basal insulin at the onset of CON would lead to a greater drop in glycemia compared to CIRC because of the higher reliance on anaerobic metabolism in the later activity. We also hypothesized that participants could accurately estimate their BG concentration during both forms of exercise.

Methods

Study Participants

The experimental protocol conformed to the standards set by the Declaration of Helsinki and is approved by the Research Ethics Board at York University. The study was registered at clinicaltrials.gov in 2017 (identifier: NCT03034798). Twelve participants with T1D were recruited for the study. All of the participants engaged in regular PA, including structured exercise and reported monitoring BG level regularly with capillary testing and a handheld glucose meter (four or more times per day). The inclusion criteria included the following: T1D

for > 1 year; on CSII for at least three months; at least in fair glycemic control (last $HbA_{1c} \leq$ 9.0% or 75 $mmol \cdot mol^{-1}$). Exclusion criteria included the following: frequent and unpredictable hypoglycemia; unable to exercise on a regular basis due to an injury; or having conditions that may make exercise unsafe (i.e. high blood pressure, late pregnancy, etc.).

Experimental Design

Participants completed a total of three exercise visits at the Human Performance Laboratory at York University. The first visit was for the determination of maximal oxygen consumption (VO_2max) followed by two visits consisting of either CON or CIRC exercise, performed in random order. Participants were asked to avoid alcohol and caffeine consumption and refrain from all forms of vigorous exercise (i.e. activities > six metabolic equivalents) for 24 hours prior to each visit. To accommodate participant scheduling, the experimental visits (CON and CIRC exercise) were conducted either in the late morning (~1100h, n = 6) or in the late afternoon (~1600h, n = 6). For each participant, the timing of both CON and CIRC visits were standardized to try and control for as many variables as possible (pre-exercise meal, time of day, and circulating insulin levels). Participants were asked to consume the same meal of their choice, at least four hours before coming to the laboratory, and take their regular insulin bolus for the meal before the exercise start time. Participants were asked to refrain from food or drink following their last meal before the exercise session, unless hypoglycemia developed (BG level < 3.9 $mmol \cdot L^{-1}$). There were no reported incidents of hypoglycemia pre-exercise for CON and CIRC conditions and it was confirmed by examining the participants' pump history that no additional insulin bolus was given after the last meal. This protocol ensured that participants arrived at the laboratory with little or no 'on-board' or active bolus insulin based on the

pharmacokinetics of their rapid acting insulin analog (119). Basal insulin rates were kept to the usual rate (100%) until the exercise start time.

Fitness Assessment (Visit 1)

During the initial visit, anthropometric measurements (height, body mass, and body fat percentage) were completed. Participants were screened for any cardiovascular complications using the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) (178). VO_2max and peak heart rate (HR) were measured using an incremental-to-maximum effort treadmill protocol. Participants also completed a supramaximal workload with increasing incline to confirm the attainment of VO_2max following a two-minute break (179). After the exercise, an enhanced Enlite™ sensor with iPro2 continuous glucose monitor (CGM) (retrospective, non real-time analysis) was placed on the abdomen using an Enlite™ Serter according to the manufacturer's instructions (Medtronic MiniMed®, Northridge, CA). Participants wore the CGM for one week and were instructed to use the glucose meter provided (Contour® Next Link, Ascensia Diabetes Care) for self-monitoring of blood glucose (SMBG) throughout the study. Following an initial calibration one hour after sensor insertion, participants were advised to calibrate four times daily with no more than 12 hours in between each calibration. The timing of the CGM placement was at least 24 hours before exercise visits 2 and 3. If visit 3 was scheduled more than one week after the VO_2max test, a new CGM was inserted at least 24 hours prior to the exercise visit.

Exercise Sessions (Visits 2 and 3)

Participants completed either 40 minutes of CON or CIRC in a randomized and counterbalanced design, with each visit separated by at least two days. Figure 3.1 represents a timeline and study design for both CON and CIRC visits. The CON visit consisted of treadmill

walking/light jogging at 40-50% of the participant's pre-determined VO_2max, while the CIRC visit included treadmill walking (four min); marching on the spot with dumbbells (45 sec); squats with front sweep (60 sec); four jumping jacks; quadruped (30 sec); two jumping jacks; four push-ups; prone forearm planks (20 sec); marching on the spot with dumbbells (30 sec); weighted ball lifts (60 sec); four push-ups; prone forearm plank (20 sec), cycling at a moderate workload (four min). This CIRC was performed three times (~13 min each time), lasting a total of 40 minutes (any time lost or gained by the participant doing the CIRC was made up for by varying the duration of cycling at the end of each CIRC.

Participants were fitted with a disposable armband (Metria™ IH1; Vancive, USA) that reports physical activity and energy expenditure throughout the study duration. For both CON and CIRC, basal insulin delivery was stopped at the onset of both exercise modalities (using the 'suspend insulin' feature) and resumed to the usual rate immediately post-exercise, as is the customary approach by many patients who exercise regularly. Capillary BG level and lactate measurements were determined approximately every 10 minutes throughout exercise using a handheld glucose meter (Contour® Next Link, Ascensia, ON, Canada) and lactate analyzer (Scout+, EKF Diagnostics, Cardiff, UK), respectively. During CON and CIRC exercise visits, participants were told their measured BG value 10 minutes prior to the onset of exercise in both CON and CIRC visits and then they were blinded to their measured glucose meter values until 20 minutes into recovery. Participants were asked to estimate their BG concentration at each measured glucose time point (i.e. every 10 minutes). The discrepancy between estimated and measured BG concentrations was assessed according to Clarke Error Grid analyses (180) (using measured and perceived BG level) and a modified Bland Altman plot (181) [(measured BG level – (estimated BG level)) / measured BG level]. If a participant developed hypoglycemia (whole

BG level of < 3.9 mmol·L^{-1}), they were instructed to stop exercising (if it was during exercise) and 16 grams of oral dextrose (Dex4®, AMG, QC, Canada) was provided.

Statistics

The BG measurements between CON and CIRC, as measured by the handheld glucose meter, were compared using two-way (time by trial) repeated measures ANOVA. Bonferroni post-hoc tests were used if significant interactions were found and statistical significance was set at $P < 0.05$, unless otherwise indicated. Participant anthropometric and descriptive characteristics were reported using mean and standard deviation. Paired t-tests were used to compare energy expenditure (in kilocalories or kcal) and percent of VO_2max during CON and CIRC. A linear regression was used to compare the measured BG concentrations with perceived BG concentrations during CON and CIRC. The percent of time spent in different BG ranges (i.e. hypoglycemia, euglycemia, and hyperglycemia) 12 hours after CON and CIRC, as measured by CGM, were compared using the Mann–Whitney test for non-parametric statistics. For this analysis, euglycemia was defined by the iPro2 CGM as a BG concentration of 3.9–10.0 mmol·L^{-1}, hypoglycemia as < 3.9 mmol·L^{-1}, and hyperglycemia as > 10.0 mmol·L^{-1}. All statistical analyses were conducted using STATISTICA 7.0 (StatSoft, USA) and GraphPad Prism software (Version 7.0). Fingerstick capillary BG level was measured with the glucose meter and used as a reference to evaluate the accuracy of the Enlite™/iPro2 CGM. The mean absolute relative difference (MARD) was calculated as the absolute relative difference between the glucose meter value and sensor value over the glucose meter value multiplied by 100. Paired t-tests were used to compare the absolute relative difference between CON and CIRC conditions pre-, during, and post-exercise.

Results

Anthropometric measurements of all participants (6 males, 6 females) are shown in Table 3.1. Most participants were young adults (mean age 32 ± 11 years [mean ± SD]), lean (body fat 21.8 ± 9.4 %,) and in good glycemic control (HbA_{1c} 7.0 ± 0.9 %). Disease duration ranged from 2-43 years and total daily insulin dose averaged 39 ± 14 U in the group. Participants were using Medtronic® (n = 6), Animas® (n = 4), or OmniPod® (n = 2) insulin pumps.

Both BG level (7.5 ± 2.6 to 9.9 ± 4.4 mmol·L^{-1}) and lactate level (1.0 ± 0.3 to 13.2 ± 4.2 mmol·L^{-1}) increased from pre to post VO_2max ($P < 0.05$ for both). Figure 3.2 shows the change in BG level from pre-exercise (-10 minutes) to recovery (+30 minutes) during both CON and CIRC visits. During the CIRC visit, pre-exercise BG level was 8.2 ± 0.4 mmol·L^{-1} (mean ± SD), dropping to 6.8 ± 0.6 mmol·L^{-1} by the end of the activity. During CON, the pre-exercise BG level was 9.5 ± 0.7 mmol·L^{-1}, dropping to 5.7 ± 0.4 mmol·L^{-1} by the end of exercise. The drop during CON was greater than the drop during CIRC in 10 of the 12 participants (83%) and for the group as a whole ($P < 0.05$). Figure 3.3 represents the mean energy expenditure (in kcal) during CON and CIRC visits (panel a) and the percent of VO_2max during CON and CIRC (panel b). On average, participants worked at a higher percent of their VO_2max during CIRC compared to CON ($P = 0.03$) and tended to expend greater energy during CIRC than in CON ($P = 0.07$). Figure 3.4 shows the lactate concentrations before, during and immediately after exercise in both visits. Lactate concentrations were significantly higher during CIRC compared to CON ($P = 0.001$ at t = 20 and t = 40, respectively).

Figure 3.5 demonstrates the accuracy of perceived to measured BG concentration via Clarke Error Grids (a) and Bland-Altman plots (b) for the two exercise sessions. Table 3.2 represents BG level estimations separated by zones A-E of the Clarke Error Grids during CON

and CIRC. These zones depict the likelihood of inappropriate treatment based on the perceived versus measured BG values.[13] Based on regression analyses and our assessment using Clarke Error Grid analyses, participants were able to more accurately estimate their BG level throughout CON (r = 0.83) compared to CIRC (r = 0.33), although both conditions showed reasonably 'safe' BG level estimations overall, with 97% of the values within zones A and B of the Clarke Error Grid (Figure 3.5). Figure 3.6 (panel a) represents the 12 hour recovery CGM data following the CON and CIRC sessions (n = 8 only because of technical limitations in data capture from CGM) and (panel b) the percentage of time spent in each of the following zones: euglycemia (3.9-10.0 mmol·L^{-1}); hypoglycemia (< 3.9 mmol·L^{-1}); and hyperglycemia (> 10.0 mmol·L^{-1}). Compared to CIRC, CON elicited greater glucose variability and led to a higher percentage of time spent in hypoglycemia post-exercise (3% vs. 10% of the time in hypoglycemia, respectively), although not significantly different (P = 0.3).

Table 3.3 shows the CGM sensor performance data during the CON and CIRC trials. Sensor performance was good overall, with MARD values all below 15% pre- during and post-exercise in both trials. However, during the exercise period itself, the MARD was significantly lower during CIRC versus CON (P = 0.03).

Discussion

It is recommended that basal insulin reductions be performed 60-90 minutes before exercise to allow for circulating insulin levels to drop by the onset of exercise (13, 14, 75). However, in reality, many individuals with T1D suspend basal insulin at the start of exercise with varying degrees of success for hypoglycemia prevention (182). This study demonstrates that with basal insulin suspension at the onset of exercise, the mean drop in BG level is greater during CON versus CIRC (P = 0.001), as seen in Figure 3.2. Similarly, Moser et al. (131) found that the

drop in BG level with intermittent high intensity exercise (IHE) was less than with CON exercise in MDI patients. Interestingly in our study, the energy expenditure (measured in kcal by the Metria IH1 armband) during exercise was similar between conditions (P = 0.07); however, the intensity of exercise, as measured by the percent of VO_2max was slightly, but significantly greater in CIRC versus CON (P = 0.03, Figure 3.3). These findings suggest that basal insulin suspension at the onset of exercise is more protective against the drop in glycemia for mixed activities when compared to activities that are primarily aerobic in nature. These findings also reveal that CON is likely a more challenging form of exercise for the development of automated insulin delivery systems that rely on single hormone therapy and technologies that trigger changes in an algorithm at the time of exercise start (like HR or accelerometry) (183).

We first performed a pilot study, in a subset of participants (n = 3), to determine if CON could be performed safely without any changes to the usual basal rate. All participants developed moderate hypoglycemia within 30 minutes of starting CON. Thus, for safety and ethical reasons, this arm of the intervention was eliminated. The failure to have data collected with 'pump on' for both CON and CIRC conditions limits our capacity to clearly demonstrate that 'pump off' reduces the risk of hypoglycemia compared to 'pump on'. However, with this study design, it was still possible for us to determine if participants respond differently to CON versus CIRC with basal insulin suspension. Another limitation in our study is that we did not include plasma free insulin measurements and this information would have provided insight regarding the impact of basal insulin suspension at the start of two different forms of exercise. A number of groups have recently demonstrated that exercise increases circulating free insulin concentrations in patients on CSII when basal insulin rates are kept constant (82), lowered (84) or suspended altogether (83) before exercise start. It is likely that increases in adipose tissue blood flow with

exercise (184) may be facilitating tissue depot uptake of insulin, which may contribute to an increased risk for exercise-associated hypoglycemia. The greater drop in glycemia during CON versus CIRC is likely related to higher levels of counterregulatory hormones released and/or greater lactate production during CIRC (87).

Al Khalifah and colleagues (185) showed that individuals with a good level of aerobic fitness (based on the norms for age and sex) are more susceptible to hypoglycemia during exercise, possibly due to their better insulin sensitivity and their higher work capacity. In our study, we terminated exercise on three occasions because of documented hypoglycemia (twice during CON; once during CIRC). However, one participant had a VO_2max of 59.8 $mL \cdot kg \cdot min^{-1}$ and the other 39.7 $mL \cdot kg \cdot min^{-1}$, so fitness level likely did not explain the incidence of hypoglycemia in our study.

Due to the increased risk for exercise-associated dysglycaemia, the usual clinical recommendation is to increase the frequency of SMBG before, during, and following PA participation (186, 187). However, it can be difficult, or undesirable at times, to perform SMBG during exercise, especially in competition where the activity must be stopped in order to 'test'. In fact, in activities such as swimming, cycling, and skydiving, it becomes incredibly challenging, and in some cases impossible, to test BG level frequently while exercising. Previous studies have assessed the accuracy of perceiving BG level in individuals with T1D (137, 177) but few have focused on exercise *per se*. Cox and colleagues (137) found that although BG level estimations were highly variable across participants, very few dangerous errors were made in estimating BG level. In another study that assessed the BG level estimation accuracy in adolescents, a poor correlation ($r = 0.35$) was found between measured and perceived BG level during 60 minutes of CON steady-state cycling exercise (188). In general, adolescents tended to underestimate their

own BG level when they were hyperglycemic and overestimate their own BG level when they were hypoglycemic during exercise. This phenomenon was also more apparent with CIRC in the present study (Figure 3.5). In the conditions of which our study was designed, the majority of participants were found to accurately estimate their own BG level during both forms of exercise when they were provided with a reference BG value 10 minutes before exercise. We also found that the accuracy of the BG level estimations was better during CON ($r = 0.83$) compared to CIRC ($r = 0.33$) (Figure 3.5). The reason for this difference is unclear, but may be attributed to the frequent variation in exercise intensities throughout the 40-minute CIRC session, which may mask the capacity to estimate BG level. Another limitation is that it is unclear how critical a reference value is for improving an individual's estimations of BG concentrations during exercise. Future studies should include a subset of participants that are not provided with a reference BG value before exercise as a comparison, or perhaps a visit in which participants are blinded to their own pre-exercise BG level.

Previous studies have investigated the accuracy of various CGM systems during IHE versus CON, although findings remain inconclusive (189-191). Bally et al. (190) found comparable CGM accuracy during IHE and CON whereas Moser and colleagues (189) revealed CGM overestimation during IHE. More recently, Taleb et al. (191) compared the performance of two current and widely used CGM systems (Dexcom G4® Platinum, Medtronic Enlite™ with MiniLink® transmitter) at rest and during exercise; finding that both products had lower performance during exercise compared to rest. Similarly in the present study, CON revealed lower performance in comparison to rest and recovery periods. The higher MARD during CON may be attributed to the more rapid drop in glycemia compared to CIRC (Table 3.3). However, based on the overall MARD values in our study, the enhanced Enlite™/iPro2 CGM performance

appears more accurate than the real-time CGM systems used in the previous study (191). The limitation with iPro2 CGM, however, is that glucose values are not reported in real-time and as such can only be used for retrospective analysis.

Numerous studies have demonstrated delayed hypoglycemia post exercise, typically occurring from 8-12 hours in recovery from prolonged activity (120, 121, 126, 192, 193). Similarly in our study, 12 hours post-exercise, the percent of time spent in hypoglycemia (defined as a sensor glucose < 3.9 $mmol \cdot L^{-1}$) was slightly higher following CON (10%) versus CIRC (3%) (P = 0.3; Figure 3.6 b). Some common suggestions to help reduce nocturnal hypoglycemia include reducing basal insulin rates overnight, reducing fast-acting insulin with the evening meal, and/or consuming low glycemic index food at bedtime, although further research in this area is required (192).

In conclusion, basal insulin suspension at the onset of exercise leads to a greater drop in glycemia during CON versus CIRC. CON also modestly increased the percent of time spent in hypoglycemia 12 hours following exercise. More effective strategies are needed to reduce the barriers associated with exercise such as the fear of hypoglycemia (113). In addition, the type of exercise performed may also impact an individual's estimations of their BG level. Following a baseline glucose meter reading, estimating BG level during exercise should be done with caution, particularly in those individuals with hypoglycemia unawareness. Both frequent SMBG and CGM use for exercise are highly recommended for active individuals with T1D to increase safety and to help with decision support from healthcare providers (13). Based on our findings that circuit-based exercise deteriorates BG level estimations compared to continuous, moderate-intensity aerobic exercise, this study supports the need for increased vigilance around monitoring BG levels during activities that are interspersed with frequent variation in exercise intensities.

Acknowledgements

This work was supported by the National Institutes of Health (NIH) / National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Grant number: 1DP3 DK101075. We would like to thank all of the participants for their enthusiasm, time, and overall contribution to research.

Author Disclosure Statement

No competing financial interests exist.

Contribution of Authors

DPZ and MCR were responsible for the conception and design of the project. AC and KT were collaborators on this project. MCR provided guidance on the data analysis, reviewed, and edited the manuscript. MCR, and VJ oversaw the data collection. DPZ and LY were responsible for the data collection and analysis. DPZ and MCR were responsible for statistical analysis, interpretation, and manuscript formulation. All authors reviewed the final manuscript prior to submission.

TABLES & FIGURES

Table 3.1: Individual anthropometric and clinical characteristics

Subject ID	**Age** (Yrs)	**Sex** (M/F)	**Height** (cm)	**Body Mass** (kgs)	**Diabetes Duration** (Yrs)	**TDD** (Units)	**Basal Insulin** (%)	**Body Fat** (%)	**VO_2max** (mL/kg/min)	**HR Peak** (bpm)	**HbA_{1c}** (%)
1	35	M	174	80.5	12	50	37	22.0	49.9	203	7.9
2	34	F	182	78.0	31	46	57	27.9	37.9	195	7.7
3	27	F	167	70.0	19	35	49	29.4	41.6	199	7.1
4	49	M	184	75.1	35	24	71	16.6	47.7	188	7.4
5	19	M	177	72.7	5	50	35	11.3	65.0	201	6.8
6	44	M	173	72.8	41	23	38	8.3	59.8	175	5.5
7	26	F	170	75.6	9	47	49	34.6	35.6	189	8.0
8	19	M	187	74.6	7	48	42	9.8	74.5	200	6.9
9	24	M	183	78.0	14	65	55	14.5	56.7	208	8.2
10	53	F	156	56.6	3	23	42	30.8	42.7	160	5.9
11	24	F	170	75.1	2	29	37	31.3	40.5	184	6.2
12	31	F	165	65.3	3	25	46	25.6	39.7	174	6.1
Mean ± SD	**32 ± 11**	**M = 6 F = 6**	**175 ± 9.1**	**72.9 ± 6.5**	**16 ± 13**	**39 ± 14**	**47 ± 11**	**21.8 ± 9.4**	**50.1 ± 13.7**	**191 ± 14**	**7.0 ± 0.9**

Note: HR, heart rate; TDD, total daily insulin dose; VO_2max, maximal oxygen consumption.

Table 3.2: Clarke error grid analyses

Zones	CON Exercise	CIRC Exercise
A	50/70 (71%)	44/70 (63%)
B	18/70 (26%)	24/70 (34%)
C	0/70 (0%)	1/70 (1%)
D	2/70 (3%)	0/70 (0%)
E	0/70 (0%)	1/70 (1%)

Note: Clarke Error Grid zones A–E during CON versus CIRC exercise. Zone A, values within 20% of the measured BG (CON 71%, CIRC 63%); Zone B, points are outside of 20%, but would not lead to inappropriate treatment (CON 26%, CIRC 34%); Zone C, points leading to unnecessary treatment (CON 0%, CIRC 1%); Zone D, points indicate potentially dangerous failure to detect hypo- or hyperglycemia (CON 3%, CIRC 0%); Zone E, points that would confuse treatment of hypo- for hyperglycemia and vice versa (CON 0%, CIRC 1%).

Table 3.3: Sensor performance data: pre-, during, and post-exercise

	CON Exercise	CIRC Exercise	*P* Value
Pre-Exercise MARD (%)	9.86 ± 0.08	8.15 ± 0.07	0.37
During Exercise MARD (%)	12.00 ± 0.12	6.96 ± 0.06	0.03 *
Post-Exercise MARD (%)	10.44 ± 0.10	10.02 ± 0.14	0.89

Note: MARD, mean absolute relative difference expressed as a percentage (%) ± SD,
*$P < 0.05$.

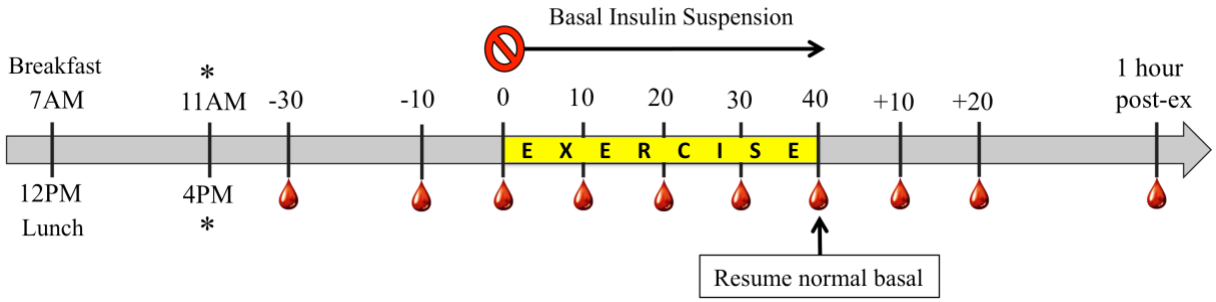


Figure 3.1: Timeline for CON and CIRC exercise sessions.

Both of the exercise sessions were conducted at either 1100 or 1600 h depending on participant availability (this was consistent for each individual). Basal insulin was suspended at the onset of both CON and CIRC exercise conditions and resumed to the normal rate immediately post-exercise (n = 12). *Arrival to laboratory.

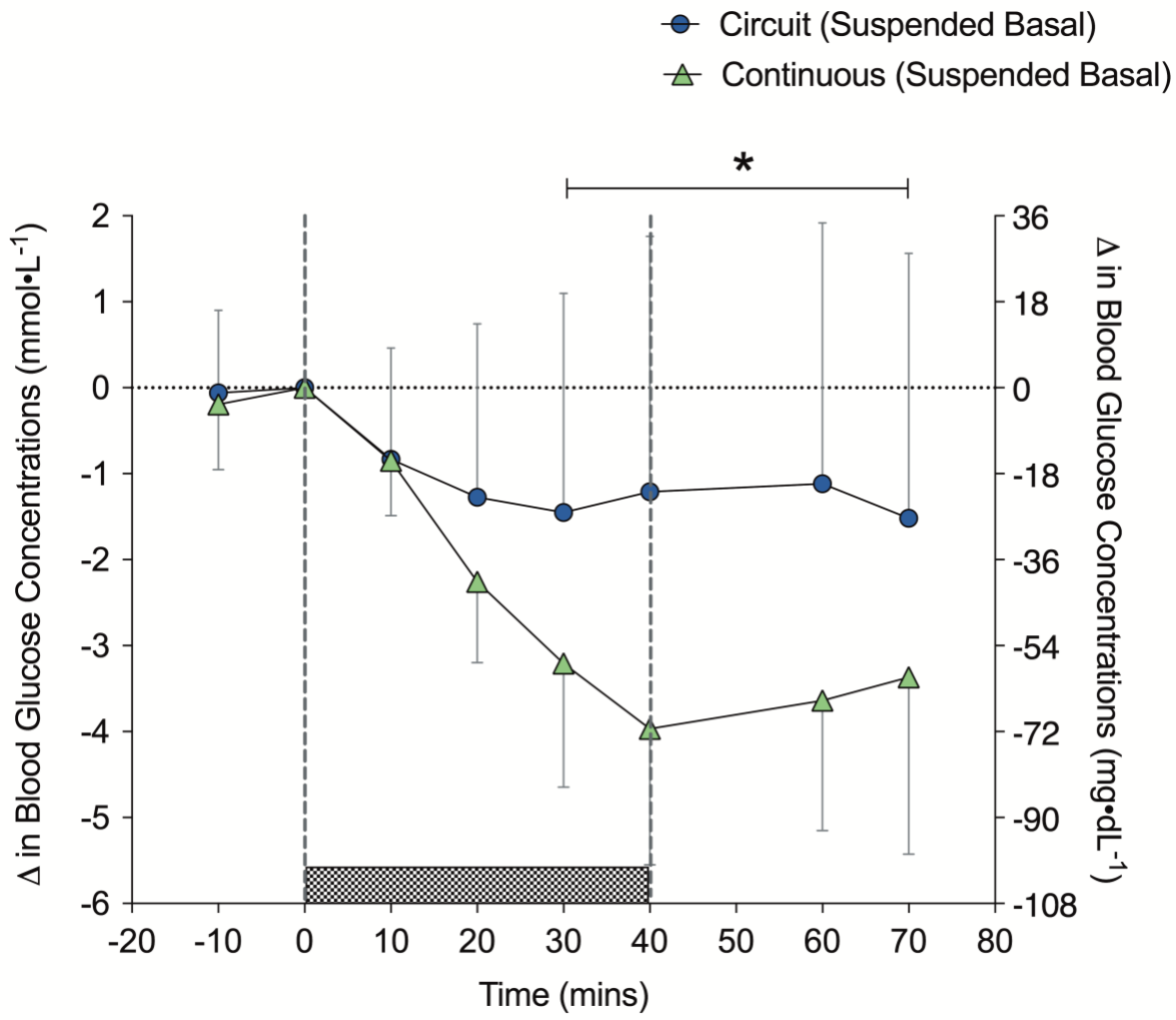


Figure 3.2: Relative change in BG concentration with exercise.

Data represents CIRC (circle) and CON exercise (triangle) pre-, during, and post-exercise. Hashed box represents the exercise session (40-min). Data are expressed relative to the BG level at the onset of exercise (time = 0). Data are expressed as mean ± SD, n = 12.

* denotes significance of $P < 0.05$.

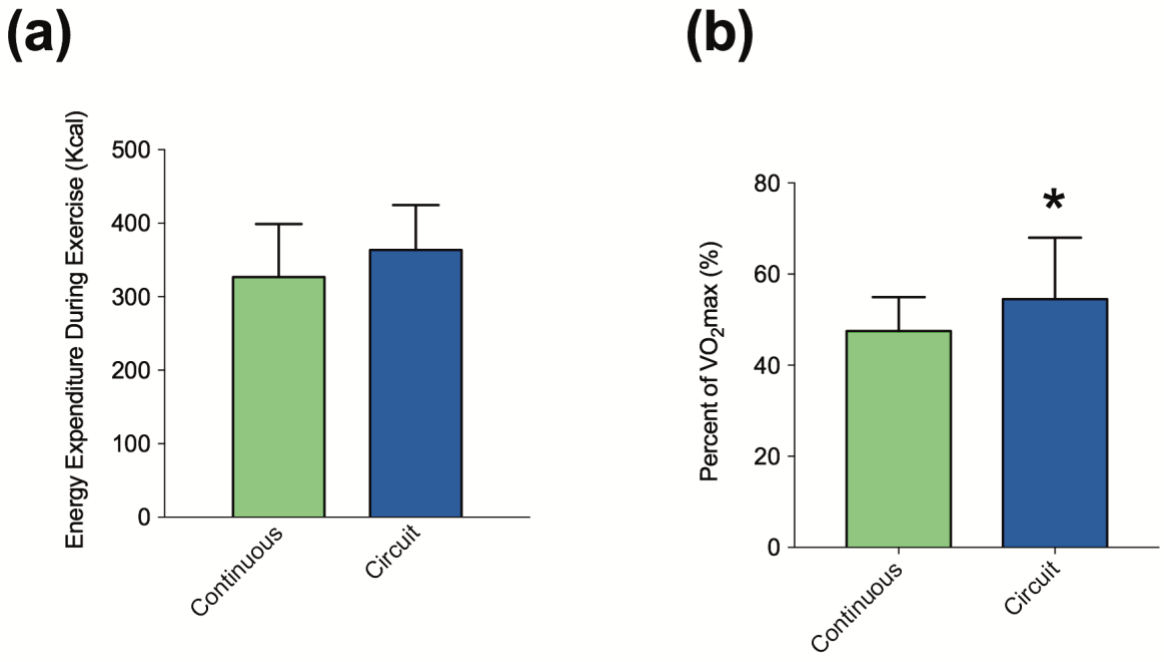


Figure 3.3: Energy expenditure and percent of VO_2max.

(a) Energy expenditure in kilocalories (kcal) during CIRC and CON exercise sessions and (b) the percent of VO_2max during CON and CIRC exercise (n = 12). Data are expressed as mean ± SD, n = 12. * denotes significance of $P < 0.05$.

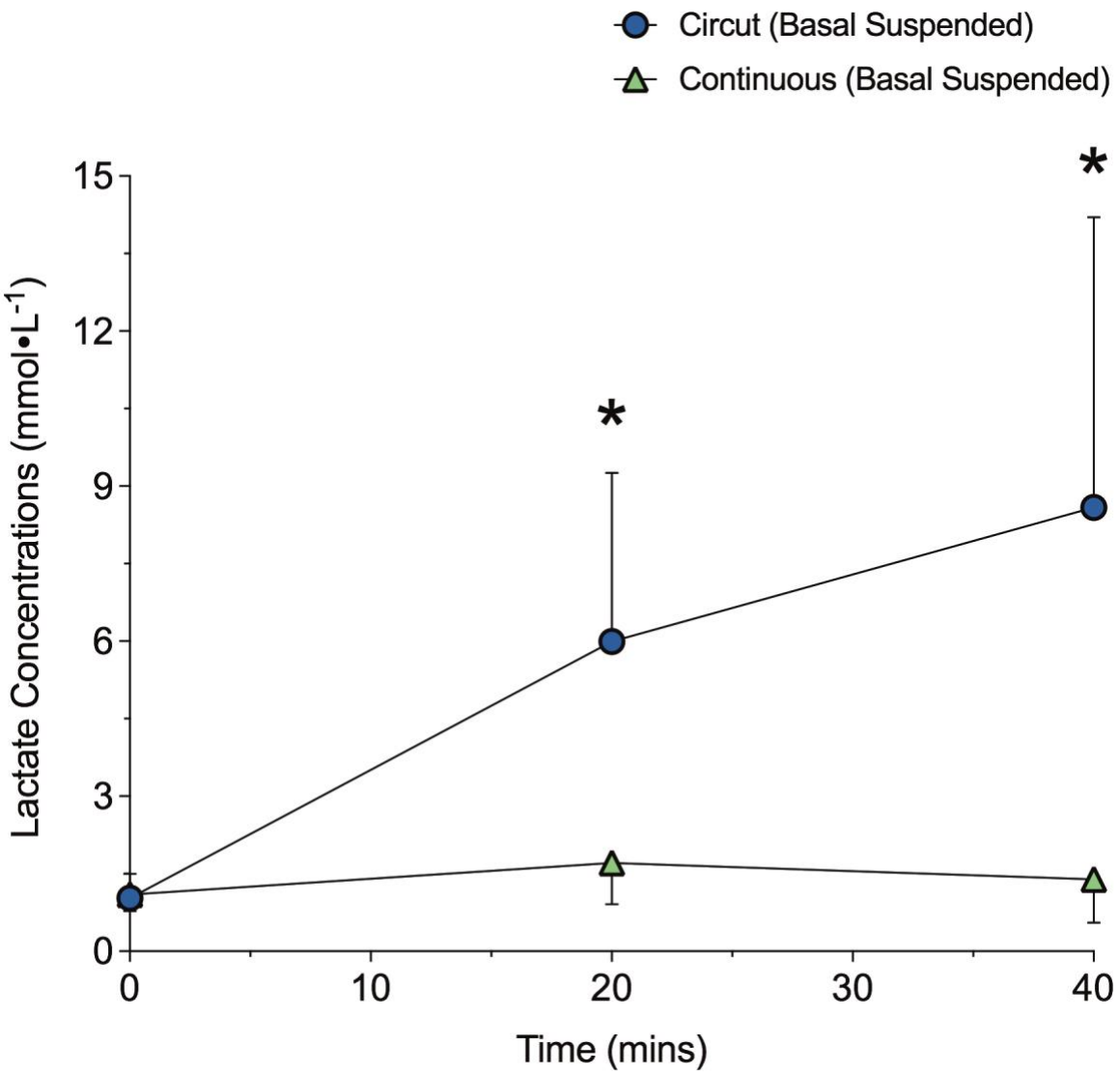


Figure 3.4: Lactate concentrations during exercise (mmol/L).

Data represents lactate level at the start (t = 0), middle (t = 20 min), and end (t = 40 min) of exercise during both CIRC and CON conditions (n = 11). Data are expressed as mean ± SD, n = 12. * denotes significance of $P < 0.05$.

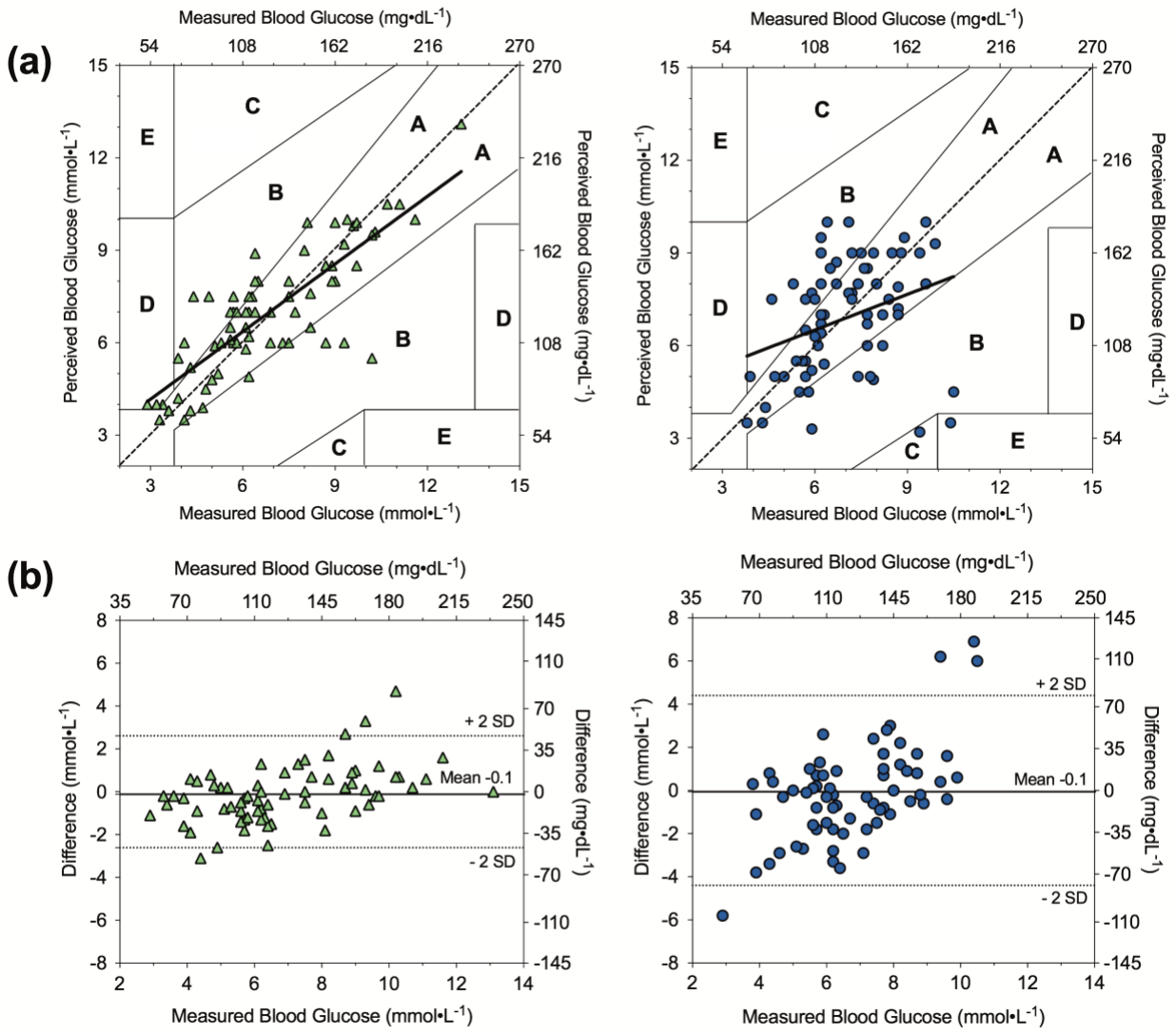


Figure 3.5: Clarke error grids and Bland-Altman plots.

(a) Clarke Error Grids comparing measured BG concentrations with perceived BG concentration during CON exercise (green triangles) and CIRC exercise (blue circles). The BG values are separated into zones A–E that represent the clinical implications of estimation errors. (b) Bland–Altman plots comparing the difference between measured and perceived BG values within two standard deviations. A BG measurement was taken 10-min before the onset of exercise and participants used this value as a reference during exercise. In general, participants could accurately estimate their BG level during exercise, particularly during CON exercise. During CON exercise, the best-fit y-intercept was 1.97 – 0.44 mmol/L and CIRC exercise y-intercept was 4.20 – 0.95 mmol/L ($P < 0.05$).

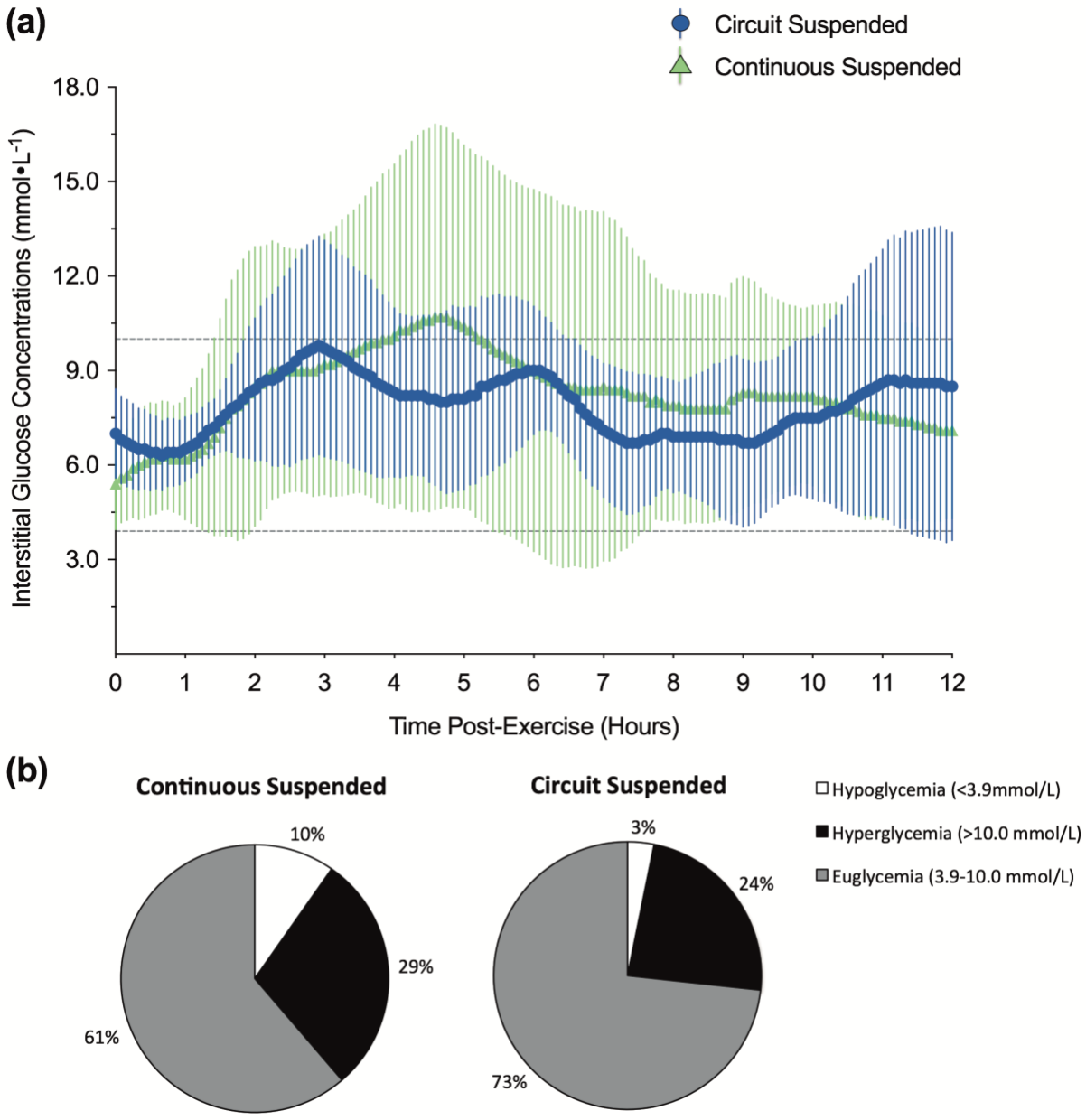


Figure 3.6: Interstitial glucose and percent time in range.

(a) Twelve-hour recovery CGM glycemia following CON (light shade) and CIRC exercise (dark shade). Data represent mean ± SD of 12 hours post-exercise from 1200–0000 or 1800–0600h. (b) Percent time spent in hypoglycemia, euglycemia, and hyperglycemia following CON versus CIRC exercise sessions (n = 8). CGM, continuous glucose monitor.

4.0 ACADEMIC PAPER 2

No disadvantage to 'pump off' versus 'pump on' during intermittent high intensity exercise and recovery in adults with type 1 diabetes.

In preparation for submission to Canadian Journal of Diabetes, 2018

No disadvantage to insulin 'pump off' versus 'pump on' during intermittent high intensity exercise and recovery in adults with type 1 diabetes.

Short title: Insulin 'pump on' versus 'pump off' during exercise

Dessi P. Zaharieva MSc [a], Ali Cinar PhD [b, c], Loren Yavelberg MSc [a], Veronica Jamnik PhD [a], and Michael C. Riddell PhD [a, d]

[a] – School of Kinesiology & Health Science, Faculty of Health, Muscle Health Research Centre and Physical Activity & Chronic Disease Unit, York University, Toronto, ON

[b] – Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL

[c] – Department of Chemical & Biological Engineering, Illinois Institute of Technology, Chicago, IL

[d] – LMC Diabetes & Endocrinology, Toronto, ON

Correspondence to:

Dr. Michael Riddell, Ph.D.

School of Kinesiology and Health Science

York University

4700 Keele Street, Toronto, ON, M3J 1P3

Keywords: Hypoglycemia, Exercise, Insulin Pump, Continuous Glucose Monitoring

Abstract

Background: A common strategy to reduce the risk of hypoglycemia during aerobic exercise in patients with type 1 diabetes is to decrease or suspend insulin delivery using continuous subcutaneous insulin infusion (CSII) pump therapy. Insulin 'pump on' has been compared to 'pump off' during prolonged walking in adolescents with type 1 diabetes, with some efficacy observed with 'pump off', although some patients developed post-exercise hyperglycemia. Intermittent high intensity exercise typically does not result in hypoglycemia in patients with type 1 diabetes and may result in post-exercise hyperglycemia. The effect of 'pump on' vs. 'pump off' during intermittent high intensity exercise is unclear. The goal of this study was to compare the impact of 'pump on' vs. 'pump off' on blood glucose concentration during an intermittent high intensity bout of exercise.

Methods: Twelve adults (six females) with type 1 diabetes using CSII and in good metabolic control (HbA_{1c} = 7.0 ± 0.9%) were recruited for the study. Participants completed a maximal aerobic capacity test, followed by two intermittent high intensity exercise bouts that were 40 minutes in duration. The two insulin adjustment strategies included 1) insulin pump set to 50% of the usual basal insulin ('pump on') or 2) insulin suspended ('pump off') for the duration of exercise, in random order. Blood glucose measurements were recorded every 10 min and after providing subjects with an initial reference glucose value, participants were blinded to their glucose and asked to estimate their levels during exercise.

Results: There were no differences in the oxygen consumption, heart rate, or energy expenditure between 'pump on' vs. 'pump off' ($P > 0.05$). Blood glucose levels were higher in 'pump off' (146 ± 22 mg/dL) vs. 'pump on' (133 ± 38 mg/dL) at exercise start ($P < 0.05$) but by the end of exercise, glucose levels were similar in 'pump off' (118 ± 36 mg/dL) vs. 'pump on'

(120 ± 46 mg/dL) (P = 0.9). Based on a regression analysis, participants were able to estimate glucose levels more accurately during 'pump on' (r^2 = 0.46) vs. 'pump off' (r^2 = 0.11). Overall, the percent time in hypoglycemia 12h post-exercise was slightly higher following 'pump on' (5 ± 8%) compared to 'pump off' (1 ± 2%), but not significantly different (P = 0.3).

Conclusion: During intermittent high intensity exercise, we found no advantage or disadvantage of 'pump on' vs. 'pump off' on glycemia. In summary, intermittent high intensity exercise can be performed with insulin 'pump on' or 'pump off' with no noticeable effect on glycemia during the activity. However, 'pump on' during intermittent high intensity exercise may increase the risk for late-onset hypoglycemia post-exercise.

Introduction

Intermittent high intensity exercise is thought to cause less of a decline in blood glucose concentration compared to aerobic exercise in patients living with type 1 diabetes because of the increase in hepatic glucose production that is stimulated by counterregulatory hormones (25). Therefore, hypoglycemia is generally more likely to occur during continuous steady state aerobic exercise as compared to intermittent high intensity exercise (116, 124). Similarly, a number of studies have demonstrated that during intermittent high intensity exercise, a decline in blood glucose concentration does still occur, particularly if the activity is performed in a non-fasted state when insulin levels may be significantly elevated (124, 174, 193, 194). As such, guidelines often recommend reducing basal insulin rates 60-90 minutes before any form of exercise (continuous steady state aerobic or intermittent high intensity exercise) that is performed for more than 30 minutes to better protect against the likelihood of hypoglycemia (13, 14).

Particularly with unplanned exercise where basal or bolus insulin adjustments cannot be made in advance of the activity, the options during exercise are limited to 1) additional carbohydrate ingestion and/or 2) basal insulin reduction at exercise onset. The Diabetes Research in Children Network (DirecNet) study group found that discontinuing basal insulin infusion (i.e. 'pump off') during 60 minutes of walking/light jogging is an effective strategy for reducing hypoglycemia in children with type 1 diabetes, but the risk of hyperglycemia is increased (176). Admon et al. (115) also compared 'pump on' (with a 50% basal rate reduction) versus 'pump off' during 40-45 minutes of unplanned continuous steady state submaximal cycling (at ~60% of VO_2max) in adolescents with type 1 diabetes and found that leaving the insulin 'pump on' had no advantage or disadvantage on glycemia during the activity, but resulted in an increased risk for late-onset hypoglycemia post-exercise. Whether 'pump on' versus 'pump off' impacts

glycemia during or after intermittent high intensity exercise in adults is unclear. Although the drop in glycemia does not appear to be as significant with intermittent high intensity or mixed exercise compared to aerobic exercise, some research suggests that it can increase the risk of delayed, nocturnal hypoglycemia (193, 195), while other studies have found no increased risk of nocturnal hypoglycemia (88, 116, 174, 196).

The primary purpose of this study was to determine the impact of 1) a 50% basal insulin rate ('pump on') versus 2) insulin pump suspension ('pump off') during 40 minutes of intermittent high intensity exercise in adults living with type 1 diabetes. The secondary outcomes were to evaluate the accuracy of estimating blood glucose level when participants were provided with their measured (actual) blood glucose value 10 minutes pre-exercise and to determine whether 'pump on' versus 'pump off' impacts nocturnal glycemia.

Methods

Study Participants

This study was approved by the Research Ethics Board at York University and was registered at clinicaltrials.gov in 2017 (identifier: NCT03034798). The 'pump off' arm of this study was previously published and includes the same set of participants (116). A total of twelve individuals (6 male, 6 female) with type 1 diabetes were recruited. All participants were on continuous subcutaneous insulin infusion (CSII) therapy for at least three months*;* in fair glycemic control (last $HbA_{1c} \leq 9.0\%$ or 75 mmol/mol*)* engaged in regular physical activity participation, and reported monitoring blood glucose levels regularly using a handheld glucose meter (four or more times per day). Exclusion criteria included frequent and unpredictable hypoglycemia, unable to exercise on a regular basis due to an injury, or having conditions that may make exercise unsafe (i.e. high blood pressure, late pregnancy, etc.).

Experimental Design

This study was a randomized crossover design that included a total of three visits in the Human Performance Laboratory at York University. During the initial visit, anthropometric data (age, height, body mass, body fat percentage, waist circumference, and blood pressure) was collected followed by a maximal oxygen consumption (VO_2max) test. Using an incremental-to-maximum effort treadmill protocol, VO_2max and peak heart rate were measured followed by a two-minute break and a supramaximal workload with increasing incline to confirm the attainment of VO_2max (179). All participants were asked to avoid alcohol and caffeine consumption and refrain from all forms of vigorous exercise (i.e. activities > six metabolic equivalents) for 24-hours prior to each study visit. The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) was used to screen participants for any complications (178).

Following the VO_2max test, participants were fitted with a professional (retrospective, non real-time) continuous glucose monitor (CGM; iPro™2, Medtronic, MiniMed®, Northridge, CA) and an Enlite™ sensor placed on the abdomen according to the manufacturer's recommendations. Participants wore the CGM for one week and were instructed to use the glucose meter provided (Contour® Next Link, Ascensia Diabetes Care, Parsippany, NJ) for self-monitoring of blood glucose (SMBG) throughout the study. The CGM was placed subcutaneously at least 24 hours prior to exercise visits 2 and 3.

To accommodate participant availability, the experimental visits were completed in the late morning (~1100h, n=6) or in the late afternoon (~1600h, n=6) and were kept consistent for each participant for the two experimental visits (i.e. pump on versus pump off, see below). Participants were asked to consume the same pre-exercise meal, of their choice, and take their

usual bolus insulin for the meal at least four hours before arriving to the laboratory to ensure little or no active bolus insulin at exercise onset. Participants were also asked to refrain from additional food consumption following their last meal before exercise, unless hypoglycemia developed ([blood glucose] < 70 $mg \cdot dL^{-1}$). If hypoglycemia developed prior to exercise, study participants were instructed to treat with 16 grams of dextrose (Dex4®, AMG Medical Inc., QC) and continue to monitor their own glucose.

All study visits were separated by at least 24 hours between experimental visits. Participants wore a disposable armband (Metria™ IH1; Vancive, USA) to measure physical activity and energy expenditure throughout the study. The experimental visits consisted of an intermittent high intensity circuit exercise session of treadmill walking (four min); marching on the spot with dumbbells (45 sec); squats with front sweep (60 sec); four jumping jacks; quadruped (30 sec); two jumping jacks; four push-ups; prone forearm planks (20 sec); marching on the spot with dumbbells (30 sec); weighted ball lifts (60 sec); four push-ups; prone forearm plank (20 sec), and cycling at a moderate intensity workload (four min). The individual circuit (~13 minutes in duration) was then repeated three times in order to achieve a total duration of 40 minutes of exercise. In recovery, participants remained seated in a chair for 30 minutes and blood glucose concentration were determined using SMBG at 20 minutes and 30 minutes post-exercise before being sent home. For both experimental visits, participants were asked to consume a similar meal of their choice and take their usual bolus insulin for the meal.

Basal Insulin Adjustments

Basal insulin rates were kept at the patients' usual rate (i.e. 100%) until exercise start time. Participants completed 40 minutes of intermittent high intensity exercise with either a) insulin pump suspended (pump off) or with b) basal insulin reduced by 50% at the onset of

exercise (pump on), in a randomized and counterbalanced fashion. In all experimental conditions, the basal insulin rate was resumed to the usual rate (i.e. 100%) immediately post-exercise. Fingerstick capillary blood glucose measurements were determined every 10 minutes throughout exercise using a handheld glucose meter (Contour® Next Link, Ascensia Diabetes Care, ON). If hypoglycemia ([blood glucose] < 70 $mg \cdot dL^{-1}$) developed during activity, the exercise was terminated immediately and participants were asked to ingest 16 grams of oral dextrose (Dex4®, AMG Medical Inc., QC). If blood glucose level did not rise above the hypoglycemic threshold by 15 minutes following dextrose treatment, this procedure was repeated until the individual's glucose level was restored. Lactate concentrations were also measured pre-exercise, during, and immediately post-exercise using a fingerstick blood sample and lactate analyzer (Scout+, EKF Diagnostics, Cardiff, UK).

Blood Glucose Estimations

For both experimental visits, capillary blood glucose level was measured 10 minutes pre-exercise and revealed to the participant. During exercise, participants were blinded to their measured blood glucose values and directed to estimate their glucose levels for each measurement (every 10 minutes of exercise). If hypoglycemia occurred during exercise, the measured blood glucose value was immediately revealed to the participant and the exercise was terminated. The discrepancy between estimated and measured glucose was assessed using a Clarke Error Grid (180) (using measured and estimated blood glucose levels) and a modified Bland Altman plot (181) [(measured blood glucose – (estimated blood glucose)) / measured blood glucose].

Statistics

Two-way repeated measures ANOVA were used to compare blood glucose levels and lactate concentrations between the pump on and pump off conditions. If hypoglycemia developed at any point during exercise, the lowest glucose value was carried out until the end of exercise for statistical analysis. A paired t-test was used to compare relative VO_2, heart rate, and energy expenditure between pump on and pump off conditions. The 12-hour recovery CGM data is represented as median and interquartile range (IQR). Using CGM analyses, the percent time spent in euglycemia (70-180 mg/dL), hypoglycemia (< 70 mg/dL), and hyperglycemia (> 180 mg/dL) was compared between both treatment arms in the 12 hours following exercise. Significant differences in the percent time in euglycemia, hyperglycemia, and hypoglycemia were compared using a Wilcoxon non-parametric test. All statistical analyses and graphs were generated using GraphPad Prism Version 7.0 (GraphPad Software, CA). All statistical significance was set *a priori* to $P < 0.05$ for all tests and data are shown as mean ± standard deviation (SD).

Results

All participants in this study were adults (32 ± 11 years of age), using insulin pump therapy (basal insulin 47 ± 11%), taking either insulin Lispro (Humalog®, Eli Lilly, Indianapolis, IN n=2) or insulin Aspart (NovoRapid®, Novo Nordisk, Bagsværd, Denmark, n=10), with a total daily insulin dose of 39 ± 14 units (0.5 ± 0.17 units/kg). Diabetes duration was 16 ± 13 years and HbA_{1c} was 7.0 ± 0.9% (53 ± 10 mmol/mol). Participants had an average VO_2max of 50.1 ± 13.7 $mL \cdot kg \cdot min^{-1}$ (range: 35.6 to 75.1 $mL \cdot kg \cdot min^{-1}$) with a peak heart rate of 191 ± 14 beats per minute. Participants' self-reported physical activity levels ranged from moderate-to-highly active.

Figure 4.1A represents the absolute blood glucose concentration from 10 minutes pre-exercise until 30 minutes post-exercise and there were no significant differences in glycemia during exercise across both conditions ($P > 0.05$). Hypoglycemia occurred in 1 of 12 participants (8%) during exercise for both 'pump on' and 'pump off' conditions. Figure 4.1B represents the relative change in blood glucose concentration from baseline until 30 minutes post-exercise in both conditions. When the data was normalized to baseline glucose (t = 0), the relative drop in glycemia was less in the 'pump on' versus 'pump off' condition from 20 minutes of exercise until 30 minutes into recovery ($P < 0.05$).

Figure 4.2A represents the mean energy expenditure expressed in kilocalories (kcals), while Figure 4.2B shows the relative work intensity expressed as a percent of VO_2max, during the two experimental sessions. The relative VO_2 was 55 ± 13% versus 55 ± 10% ($P = 0.6$) and the estimated energy expenditure during the 40-minute exercise bout was 376 ± 52 kcal versus 363 ± 61 kcal ($P = 0.6$) in 'pump on' and 'pump off' arms, respectively.

Figure 4.3 represents the lactate concentrations pre-exercise, in the middle of exercise, and immediately post-exercise for both treatment conditions. There was a significant increase in lactate levels from the start to the end of exercise ($P < 0.05$), but there was no difference between conditions.

Figure 4.4A represents a Clarke error grid comparing the measured blood glucose versus estimated glucose concentration during pump on and pump off exercise arms. Based on the regression analysis for the Clarke Error Grid, participants were able to more accurately estimate their blood glucose concentration during the 'pump on' condition ($r^2 = 0.46$) compared to 'pump off' ($r^2 = 0.11$) condition. Figure 4.4B represents the Bland-Altman plots for measured versus perceived glucose levels during both 'pump on' and 'pump off' exercise conditions. With 'pump

on' during exercise, there was a positive bias (18 ± 56 mg/dL) and therefore, on average, the measured blood glucose level was higher than the perceived blood glucose level of patients (P = 0.01). However, there was no significant bias with 'pump off' during exercise (2 ± 71 mg/dL).

Table 4.1 demonstrates the blood glucose concentration (estimated versus measured) as a percent of time spent in each zone (A–E) of the Clarke Error Grid during 'pump on' and 'pump off' conditions. These zones describe the likelihood of inappropriate treatment based on the estimated glucose values using measured blood glucose values as the reference (180). Based on the Clarke error grid analysis, participants tended to be more accurate at estimating blood glucose concentrations during exercise with 'pump off' compared to 'pump on' (97% vs. 91% of values in zones A and B; P = 0.05, Chi-square).

Figure 4.5A demonstrates the interstitial glucose 12-hour recovery data from 1200–0000h or 1800–0600h for 'pump on' and 'pump off' exercise sessions. Due to technical issues with the data upload of multiple CGM devices, the 12-hour recovery data represents only a subset of study participants (n = 7). The CGM values reported as mean ± SD (median, IQR) were 158 ± 54 (157, 109-200) mg/dL and 145 ± 32 (144, 111-178) mg/dL in the 'pump on' and 'pump off' conditions, respectively (P = 0.4). Figure 4.5B represents the percent time spent in euglycemia (70-180 mg/dL), hyperglycemia (> 180 mg/dL), and hypoglycemia (< 70 mg/dL) in the 12 hours following exercise across both conditions. The mean percent time spent in euglycemia during the 12-hour recovery period was 61 ± 32% in the 'pump on' condition versus 72 ± 16% in the 'pump off' condition (P = 0.3). The average percent time spent in hyperglycemia was 34 ± 35% versus 27 ± 16% in the 'pump on' compared to 'pump off' treatment arms (P = 0.7). The percent time spent in hypoglycemia was slightly higher following 'pump on' (5 ± 8%) compared to 'pump off' (1 ± 2%), but this difference was not statistically significant (P = 0.3).

Discussion

For patients with type 1 diabetes, the duration, timing, intensity of exercise, active insulin in the circulation, and previous carbohydrate intake are just some of the factors that need to be considered and can impact the insulin dosing strategy necessary to maintain euglycemia during exercise (13). Maintaining blood glucose concentration in a target range remains an ongoing challenge in diabetes management, particularly for those individuals that do not plan in advance of physical activity and exercise. According to recent exercise guidelines for type 1 diabetes in children and adults (13, 78), significant pre-planning is necessary to improve the time spent in an optimal glucose range and decrease the risk of hypoglycemia during exercise. For example, reductions in basal insulin are recommended as early as 60-90 minutes pre-exercise (2, 13, 14, 78) and additional basal rate adjustments may be necessary based on personal experiences (197). Interestingly, based on the current techniques used pre-, during, and post-exercise, Pinsker et al. (182) reported that most people adjust insulin needs and carbohydrate intake around exercise start time, but often still reported experiencing hypoglycemia following exercise. Maintaining blood glucose concentration in a target range remains an ongoing challenge in diabetes management, particularly for those individuals that do not plan in advance of exercise.

In this study, we demonstrate that there was no advantage or disadvantage to leaving the 'pump on' versus 'pump off' *during* 40 minutes of intermittent high intensity exercise (no significant differences). When the data are represented as absolute glucose concentrations, no significant differences were found during intermittent high intensity exercise between both 'pump on' and 'pump off' conditions. However, when the data are normalized to baseline blood glucose (Figure 4.1B), the relative drop in glycemia from the start to the end of exercise was less in the 'pump on' versus 'pump off' conditions (12 mg/dL versus 28 mg/dL, $P = 0.002$). For

unknown reasons, at exercise start, the average blood glucose concentration was lower in the 'pump on' versus 'pump off' condition (133 ± 38 mg/dL versus 146 ± 23 mg/dL, respectively; $P < 0.05$).

In both insulin pump conditions, hypoglycemia occurred in 1/12 (8%) participant's during exercise. Although there were no significant differences observed in blood glucose concentrations during exercise, the 'pump on' versus 'pump off' percent time spent in hypoglycemia in the 12-hour period following exercise varied slightly (5% in 'pump on' versus 1% in 'pump off', $P = 0.3$). In the 12-hour recovery period following exercise, a total of 4/7 (57%) participants experienced hypoglycemia in the 'pump on' condition versus 1/7 (14%) in the 'pump off' condition. Therefore, reducing basal insulin by 20% at bedtime, or the consumption of a bedtime snack, may still be required to help protect against nocturnal hypoglycemia following high intensity interval exercise, especially in cases where insulin infusion is not suspended during exercise (13).

Some patients with diabetes make a claim that they can estimate their glucose level during exercise and that they know if hypoglycemia or hyperglycemia is developing. To examine this possibility, we compared the measured glucose concentration to estimated blood glucose during exercise using a Clarke error grid analysis. We found that participants were indeed able to estimate glycemia fairly accurately during both 'pump on' and 'pump off' exercise conditions (91% and 97% of values in zones A and B for 'pump on' vs. 'pump off', respectively), although for unclear reasons the accuracy did improve slightly when the pump was removed.

A number of limitations exist in this study that are important to mention. First, this study included a small sample size of participants with diabetes, in good metabolic control, with relatively high fitness levels based on their pre-determined VO_2max. As such, our findings may

not translate well across a larger population of patients living with type 1 diabetes that may be in poor metabolic control and have lower fitness levels. Second, we compared intermittent high intensity exercise with pump on versus pump off; however, did not keep the time of day consistent between the study participants, although the time of day for exercise was consistent within patients. Studies have shown that morning versus afternoon exercise can impact glycemia differently (144, 198), with the latter placing a greater risk for hypoglycemia in late recovery. Third, the exercise was 40 minutes in duration and therefore, it would be valuable for future studies to assess intermittent high-intensity exercises of both shorter and longer duration to better understand if 'pump on' versus 'pump off' impact glycemic outcomes in a wider variety of exercise durations and intensities. Finally, due to technical issues with the data upload of multiple CGM devices, the 12-hour recovery data represents only a small subset of study participants (n = 7). We also did not standardize the meals post-exercise and this may have contributed to the glycemic excursions that are apparent in the 12-hour recovery data.

In summary, during a 40-minute bout of intermittent high intensity exercise, there were no significant differences in blood glucose concentrations with 'pump on' as compared to 'pump off'. Although high intensity exercise has been shown to cause less of a decline in blood glucose level when compared to aerobic exercise in some studies (124), the former can be associated with a significant the drop in glycemia that places individuals at risk for hypoglycemia (174, 193). Interestingly, during exercise, although absolute blood glucose levels were not significantly different between trials, there was a slightly higher percent time spent in hypoglycemia overnight in the 'pump on' treatment arm. Therefore, insulin pump suspension ('pump off') during intermittent high intensity exercise can be implemented for at least 40 minutes without impacting acute glycemia and may be associated with less post-exercise, late-onset hypoglycemia.

Acknowledgements

This work was supported by the National Institutes of Health (NIH) / National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Grant number: 1DP3 DK101075. We would like to thank all of the participants for their enthusiasm, time, and overall contribution to research.

Contribution of Authors

DPZ, MCR, and VJ were responsible for the conception and design of the project. MCR, and VJ oversaw the data collection. DPZ and LY were responsible for the data collection and analysis. DPZ and MCR were responsible for statistical analysis, interpretation, and manuscript formulation. All authors reviewed the final manuscript prior to submission.

Author Disclosure Statement

DPZ has received speaker's honoraria from Medtronic Diabetes and Ascensia Diabetes. MCR has received speaker's honoraria from Medtronic Diabetes, Insulet Corporation, Ascensia Diabetes, Novo Nordisk (via JDRF PEAK Program), Xeris Pharmaceuticals, Lilly Diabetes, and Lilly Innovation. No other potential conflicts of interest relevant to this article were reported.

TABLES & FIGURES

Table 4.1: Clarke Error Grid Analysis

Zones	'Pump On' Exercise	'Pump Off' Exercise
A	41/70 (58%)	44/70 (63%)
B	23/70 (33%)	24/70 (34%)
C	0/70 (0%)	1/70 (1%)
D	6/70 (8%)	0/70 (0%)
E	0/70 (0%)	1/70 (1%)

Note: Clarke Error Grid zones A-E during 'pump on' vs. 'pump off' exercise conditions. Zone A = Values within 20% of the measured blood glucose *('Pump On' 58%, 'Pump Off' 63%)*, Zone B = Points are outside of 20%, but would not lead to inappropriate treatment *('Pump On' 33%, 'Pump Off' 34%),* Zone C = Points leading to unnecessary treatment *('Pump On' 0%, 'Pump Off' 1%),* Zone D = Points indicate potentially dangerous failure to detect hypo- or hyperglycaemia *('Pump On' 8%, 'Pump Off' 0%)*, Zone E = Points that would confuse treatment of hypo- for hyperglycaemia and vice versa *('Pump On' 0%, 'Pump Off' 1%).*

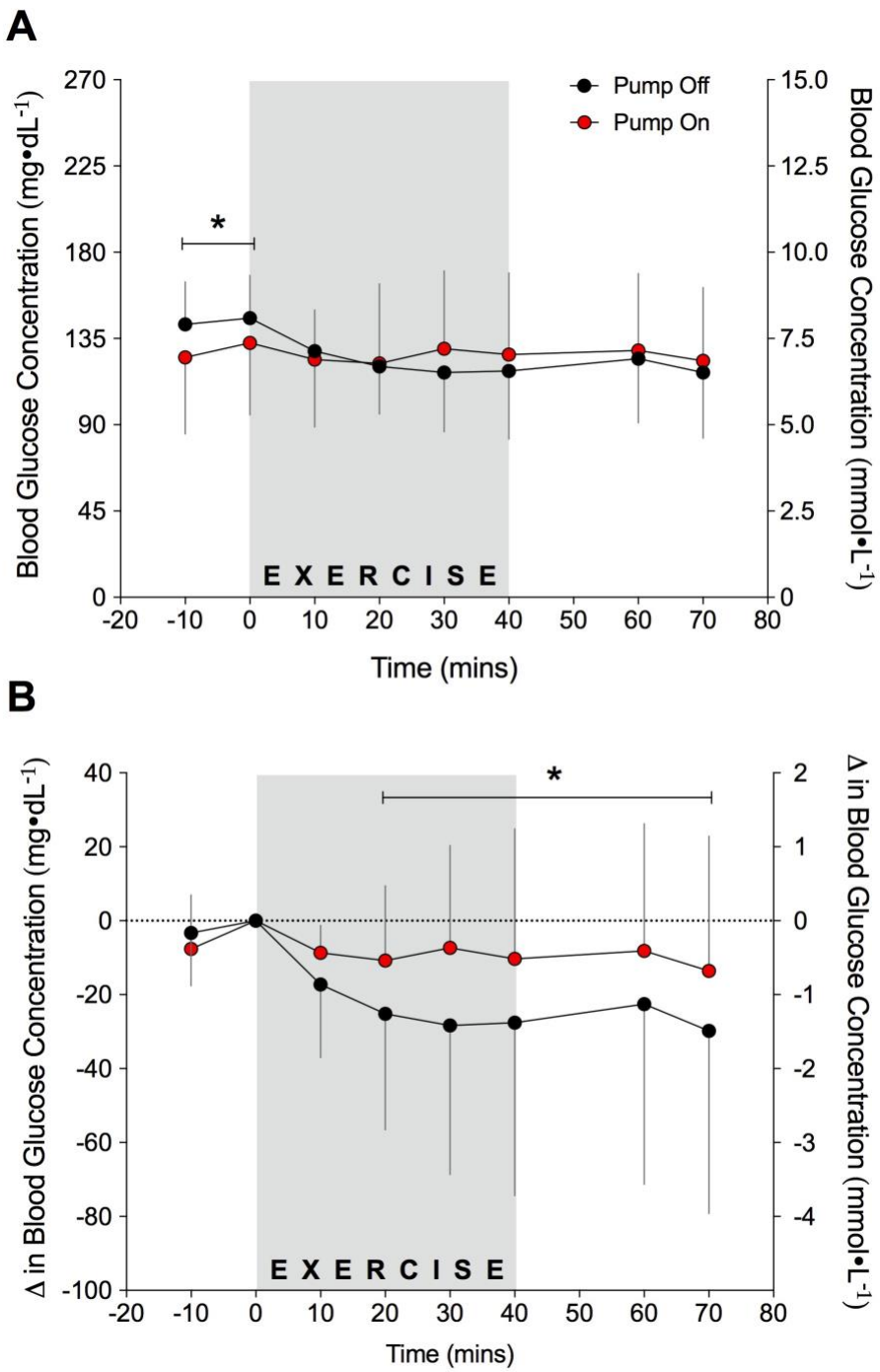


Figure 4.1: Absolute and relative change in blood glucose concentration.

A, data represents absolute blood glucose levels from 10 mins pre-exercise to 30 minutes post-exercise. B, data represents relative change in blood glucose during 'pump on' and 'pump off' conditions. Black represents 'pump off' condition. Red represents 'pump on' condition. Data represents mean ± SD, n = 12.

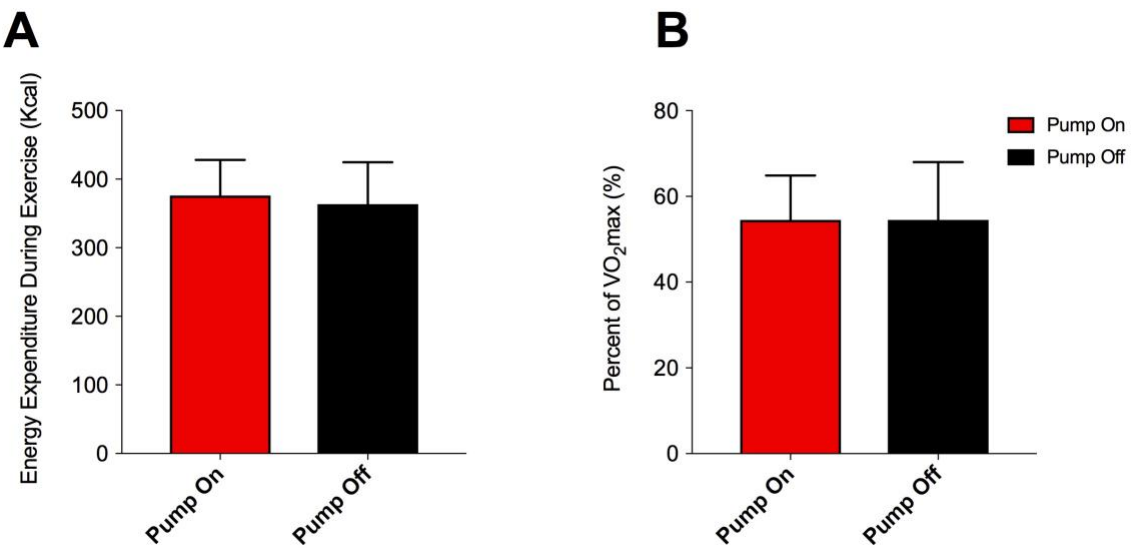


Figure 4.2: Energy expenditure and percent of VO_2max.

A, Energy expenditure in kilocalories (kcal) over 40 minutes of high intensity interval exercise with 'pump on' versus 'pump off' and B, the relative work rate as percent of VO_2max during 'pump on' versus 'pump off' exercise conditions (n = 12). Data represent mean ± SD.

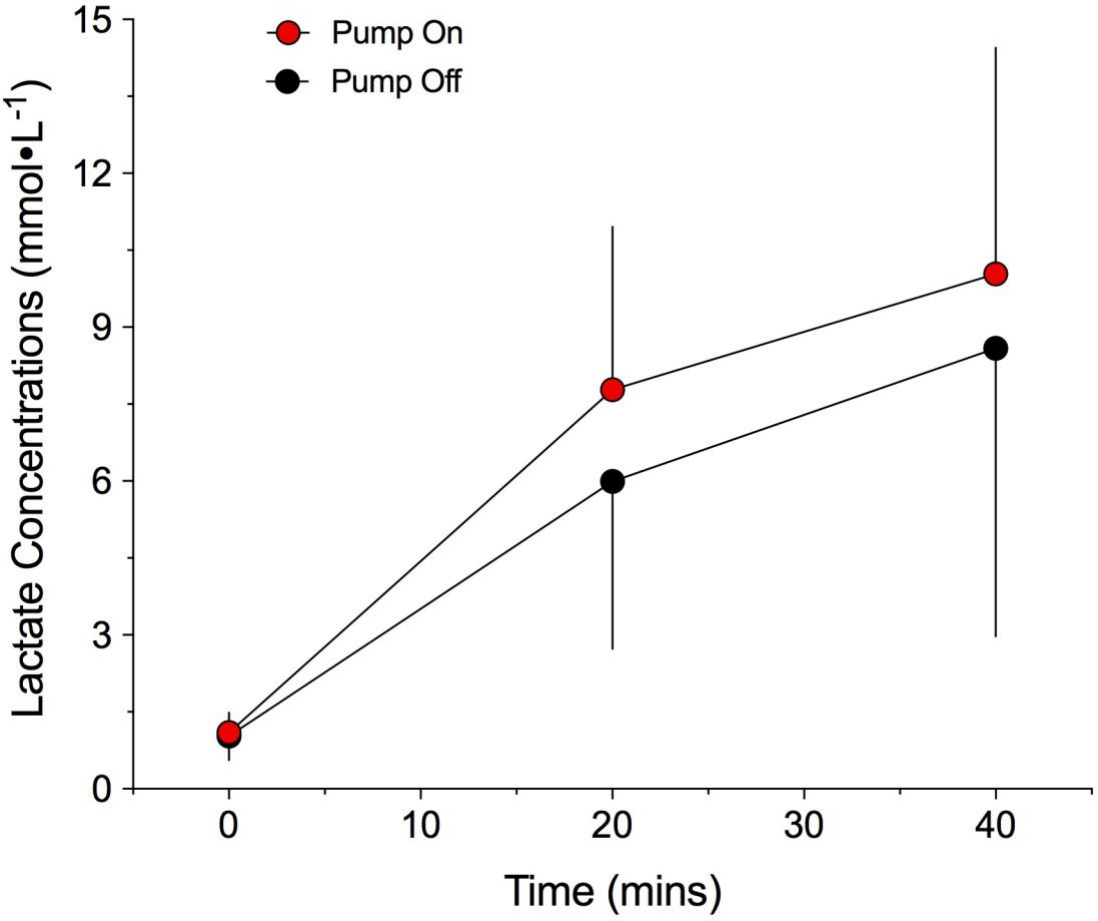


Figure 4.3: Lactate concentrations with pump on vs. pump off (mmol/L).

Data represents lactate levels at the start (t = 0), middle (t = 20 min), and end (t = 40 min) of exercise during both 'pump on' (red) and 'pump off' (black) conditions (n = 10). Data represent mean ± SD.

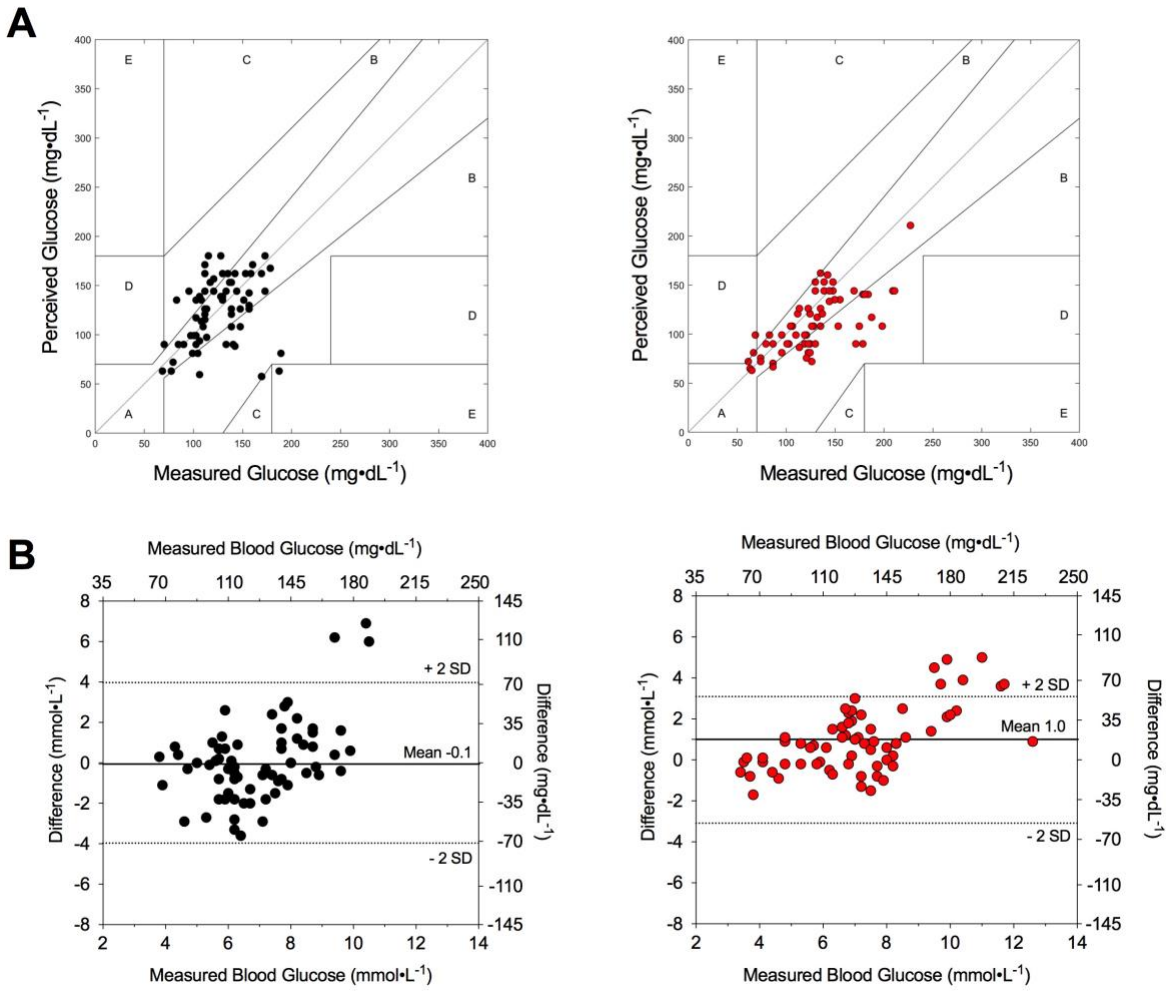


Figure 4.4: Clarke error grids and Bland-Altman plots.

A, Clarke error grids comparing measured blood glucose concentration with estimated glucose concentration during intermittent high intensity exercise with 'pump off' (black) and 'pump on' (red). The blood glucose values are separated into zones A–E that represent the clinical implications of estimation errors. B, Bland–Altman plots comparing the difference between measured and estimated glucose values within two standard deviations. A blood glucose measurement was taken 10-mins before the onset of exercise and participants used this value as a reference during exercise.

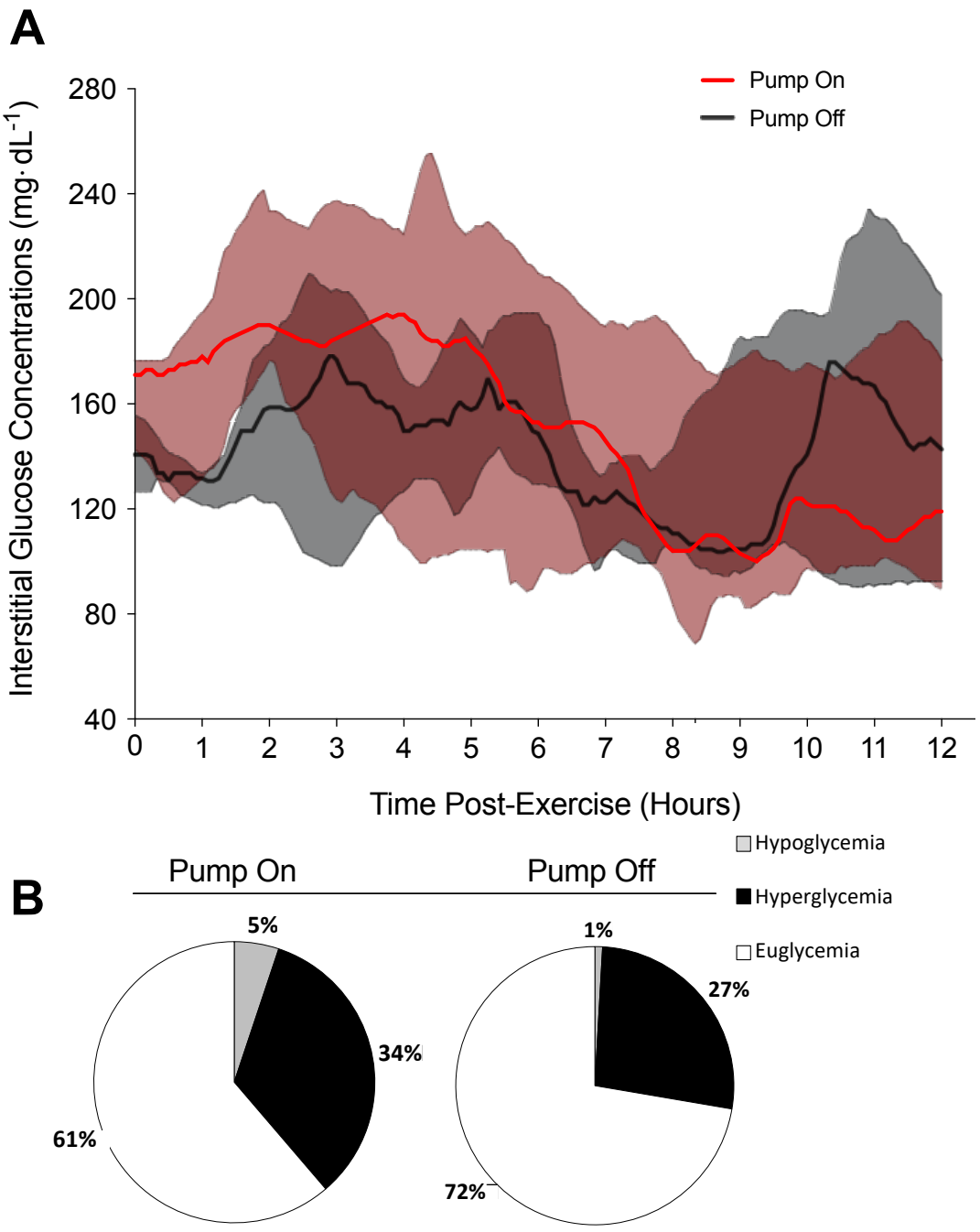


Figure 4.5: Interstitial Glucose and Percent Time in Range.

A represents the 12-hour recovery CGM data following 'pump on' (red) condition and 'pump off' (black) condition. Data represent median and interquartile range of 12-h post-exercise from 1200–0000 or 1800–0600h. B represents percent time spent in hypoglycemia, euglycemia, and hyperglycemia following 'pump on' and 'pump off' (n = 7) conditions. CGM, continuous glucose monitor.

5.0 ACADEMIC PAPER 3

Optimized open-loop glucose control and time in range with basal insulin reduction 90 minutes before aerobic exercise in patients with type 1 diabetes on continuous subcutaneous insulin infusion.

Returned with Minor Revisions to Diabetes Care, 2018

Optimized open-loop glucose control and time in range with basal insulin reduction 90 minutes before aerobic exercise in patients with type 1 diabetes on continuous subcutaneous insulin infusion.

Short Title: Basal insulin management for exercise in CSII

Dessi P. Zaharieva (M.Sc.)*[1], Sarah McGaugh (B.Sc.)[1], Rubin Pooni (B.Sc.)[1], Todd Vienneau (B.Sc.)[2], Trang Ly (MBBS, FRACP, Ph.D.)[3], & Michael C. Riddell (Ph.D.) [1, 4]

[1] – School of Kinesiology & Health Science, Muscle Health Research Centre, Faculty of Health, York University, Toronto, ON, Canada

[2] – Insulet Canada Corporation, Oakville, ON, Canada

[3] – Insulet Corporation, Billerica, Massachusetts, USA

[4] – LMC Diabetes & Endocrinology, Toronto, ON, Canada

Correspondence to:

Dr. Michael Riddell, Ph.D.

School of Kinesiology and Health Science

York University

4700 Keele Street, Toronto, ON, M3J 1P3

Keywords: Basal Rate, Hypoglycemia, Exercise, Continuous Glucose Monitoring, Continuous Subcutaneous Insulin Infusion, Type 1, Insulin Pump, Aerobic Exercise, Basal Insulins, Real-Time Continuous Glucose Monitoring, Hypoglycemia Prevention and Exercise, Blood Glucose Self-Monitoring

Abstract

Background: For individuals with type 1 diabetes on continuous subcutaneous insulin infusion (CSII), strategies to reduce exercise-associated hypoglycemia typically include basal rate reduction (BRR) and/or carbohydrate feeding, although the timing and amount of BRR necessary to prevent hypoglycemia is unclear. The goal of this study was to determine if a BRR set 90 minutes pre-exercise can better attenuate hypoglycemia vs. pump suspension at exercise onset. **Methods:** Seventeen individuals (13 females) with type 1 diabetes completed three 60-minute treadmill exercise (~50% of VO_2peak) visits in a randomized crossover design. The insulin strategies included: a) pump suspension at exercise onset; b) 50% BRR set 90 minutes pre-exercise; and c) 80% BRR set 90 minutes pre-exercise. **Results:** With no significant difference in starting blood glucose across all conditions (P>0.05), the 80% BRR was associated with the smallest reduction in glycemia during exercise (P=0.01). With pump suspension at exercise onset, 7/17 participants developed hypoglycemia vs. 1/17 in the BRR conditions (P<0.05). Following a standardized meal post-exercise, glucose rose in the pump suspension and 50% BRR (both P<0.05), but failed to rise in the 80% BRR condition (P=0.16). Based on interstitial glucose, overnight percent time in range was 83±7%, 83±6%, and 78±8% and percent time in hypoglycemia was 2±2%, 1±1%, 5±3% for 80% BRR, 50% BRR, and pump suspension, respectively (P>0.05). **Conclusion:** Overall, a 50-80% BRR set 90 minutes pre-exercise optimizes open-loop glucose control and decreases hypoglycemia risk during exercise better than pump suspension at exercise onset, while not compromising the post-exercise meal overall glucose control.

Introduction

In order to maintain blood glucose homeostasis during exercise, circulating insulin concentration normally decreases and glucagon levels increase to promote hepatic glucose production (199). However, in individuals with type 1 diabetes, due to the absolute destruction of the insulin-producing beta cells in the pancreas, patients become dependent on exogenous insulin via multiple daily injections or continuous subcutaneous insulin infusion (CSII) (16). CSII therapy uses only short-acting insulin for both continuous basal insulin infusion (regulates your glucose levels in between meals) and bolus insulin infusion (often taken before a meal or to correct hyperglycemia) (1). In this patient population, specifically during aerobic exercise, insulin levels tend to not drop fast enough, even if insulin delivery is suspended, and there may be an attenuated glucagon response (13). In fact, individuals living with type 1 diabetes can have increased circulating exogenous insulin levels during exercise, either when subcutaneous basal insulin infusion rates are held constant (82) or even if a temporary basal rate reduction (BRR) is set one-hour before exercise (84).

For active individuals with type 1 diabetes, common strategies to help reduce the risk of hypoglycemia include increasing carbohydrate ingestion before or during exercise (200, 201), reducing the pre-meal bolus insulin dose (123, 202), and/or performing a BRR before exercise onset (83, 84, 117). General exercise guidelines for open-loop insulin delivery suggest BRR at least 60-90 minutes before the onset of exercise, with little evidence to substantiate the recommendation (13, 14, 119, 203). In reality, patients often disconnect or suspend insulin infusion at exercise start and resume basal insulin immediately post-exercise (182). This may be in part due to forgetting to set a BRR pre-exercise, participating in unplanned exercise, or trying to prevent post-exercise rebound hyperglycemia. Pump suspension appears to be effective in

limiting hypoglycemia during circuit exercise, but may not be that effective in eliminating the drop in glycemia during aerobic exercise (115, 116). The DirecNet study group showed that in a pediatric population (n=49), insulin pump suspension at the start of a 75-minute aerobic exercise bout attenuated the drop in glycemia compared to no pump suspension, but it did not completely eliminate hypoglycemia risk and promoted increased hyperglycemia risk post-exercise (204). Franc et al. (83) suggested that without additional carbohydrates, the most effective strategy to reduce hypoglycemia for 30 minutes of spontaneous exercise is an 80% BRR (i.e. 20% of the usual basal rate) throughout activity and for two hours post-exercise, although a significant drop in glycemia should still be expected. Thus, pump suspension at exercise onset may attenuate the drop in glycemia, but does not protect against hypoglycemia during aerobic exercise and leaving the pump suspended or disconnected in recovery in many cases appears to contribute to post-exercise hyperglycemia (83).

The study objective was to determine which BRR strategy best attenuates the drop in glycemia during prolonged aerobic exercise in patients with type 1 diabetes using CSII. The change in glucose was examined for the exercise period and for two hours following a standardized meal post-exercise. This study is referred to as the Omnipod® Type 1 diabetes Insulin Management for Exercise (OmniTIME) Study.

Methods

Study Participants

The experimental protocol conformed to the standards set by the Declaration of Helsinki and was approved by the Research Ethics Board at York University. The study was registered at clinicaltrials.gov in 2017 (identifier: NCT03130101). Enrollment criteria included participants 17-65 years of age, duration of diabetes > one year; on CSII > one month (total daily dose of at

least 0.25 U/kg); and last $HbA_{1c} \leq 9.9$ % or 85 mmol/mol. All participants were using Omnipod® Insulin Management System (Insulet, Billerica, MA) and either insulin lispro (Humalog®, Eli Lilly, Indianapolis, IN n=5) or insulin aspart (NovoRapid®, Novo Nordisk, Bagsværd, Denmark, n=12). Exclusion criteria included frequent and unpredictable hypoglycemia; unable to exercise regularly due to an injury; having conditions that may make exercise unsafe (i.e. high blood pressure, late pregnancy, etc.); and/or physician diagnosis of active diabetic retinopathy or neuropathy. Written informed consent was obtained from all participants before study initiation.

Fitness Assessment (Visit 1)

Anthropometric measurements including height, body weight, blood pressure, and body fat percentage were completed during the initial assessment. Participants were asked to complete a Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) to screen for any cardiovascular complications (178). Once cleared to exercise, participants completed the International Physical Activity Questionnaire – Short Form (IPAQ-SF) based on self-reported activity. Participants were also asked to complete Gold (205) and Clarke (206) questionnaires to categorize hypoglycemia awareness. Using an incremental-to-maximum effort treadmill protocol, VO_2peak and peak heart rate were measured with a portable metabolic unit (K5, COSMED, Rome, Italy) and heart rate monitor (Polar Electro, Kemple, Finland).

Participants wore a continuous glucose monitoring (CGM) device (Dexcom G4® or G5®, San Diego, CA) on the abdomen or arm according to the manufacturer's instructions and were instructed to use their Personal Diabetes Manager (PDM; Omnipod®, Insulet, Billerica, MA) for self-monitoring of blood glucose (SMBG) with the associated blood glucose test strips (FreeStyle Lite, Abbott, Laboratories, Chicago, IL) and for CGM calibrations whenever necessary throughout the study.

Experimental Visits (Visits 2-4)

Participants were asked to avoid alcohol and caffeine consumption and refrain from all forms of vigorous exercise (i.e. activities > six metabolic equivalents) for 24 hours prior to each visit. Female participants were not tested during the luteal phase because research suggests that estrogen levels are higher particularly during this phase of the menstrual cycle and this may impact fuel selection by increasing the rate of fat utilization (207). Participants were asked to consume the same lunch of their choice for each visit with their usual mealtime bolus insulin no later than 11:30AM and to refrain from consuming additional food or drink following the lunchtime meal, unless hypoglycemia (< 70 mg/dL) developed. Participants completed the following BRR strategies in a randomized crossover fashion: a) pump suspension (i.e. 0% of basal insulin) for the duration of activity, starting at the onset of exercise; b) a 50% BRR (i.e. 50% of basal insulin), set 90 minutes in advance of exercise for the duration of activity; and c) an 80% BRR (i.e. 20% of basal insulin), set 90 minutes in advance of exercise for the duration of activity. Based on the recent exercise consensus statement (13), blood glucose targets for exercise were between 70-360 mg/dL. Using SMBG, participants were asked to monitor their glucose levels 90 minutes before exercise start time. If glucose values were between 70-90 mg/dL, 8g of dextrose was recommended to help achieve glycemic target. If blood glucose was > 270 mg/dL, blood ketones were tested (FreeStyle Precision Neo, Abbott Laboratories, Abbott Park, IL) and exercise could proceeded if levels were < 0.6 mmol/L. The principal student investigator phoned each participant at ~1:30PM as a reminder to set BRR to the appropriate amount for the study duration depending on the condition (i.e. perform a 50% or 80% BRR until the end of exercise). Participants arrived at the laboratory no later than 2:30PM and began exercise at 3:00PM for all conditions. Participants had no active or 'on-board' insulin at exercise

onset and this was confirmed by examining their pump history to ensure that no additional insulin was given following the lunchtime bolus. The experimental visits consisted of 60 minutes of treadmill walking/light jogging at 45-55% of the participant's pre-determined VO_2peak and all visits were separated by at least 24 hours. The exercise was divided into four 15-minute bouts with 5-minute rest periods in between, similar to previous research (81). Substrate oxidation rates (i.e. fat and carbohydrate) were calculated using the expired gas collection during the last 5 minutes of the first and last bouts of exercise (208).

Capillary fingerstick blood glucose measurements were determined every 15 minutes throughout exercise using a standardized laboratory glucose meter (Contour® Next Link, Ascensia Diabetes Care, Parsippany, NJ). This blood glucose-monitoring device has a high level of accuracy as compared to a laboratory standard (209) and we regularly performed quality control tests using the control solution provided by the manufacturer. All glucose measurements were completed in duplicate and repeated if the values differed by > 10 mg/dL. If a participant developed hypoglycemia (< 70 mg/dL) based on SMBG, they were instructed to stop exercising (if it was during exercise) and an initial 16 grams of oral dextrose (Dex4®, AMG Medical Inc., QC, Canada) was provided. If exercise was suspended due to hypoglycemia, participants returned to the treadmill to complete the exercise portion only once blood glucose concentration reached > 81 mg/dL. For the analysis, the change in glucose was calculated based on the participants' glucose value at exercise start and the last value measured immediately at the end of exercise, according to the following:

Change in glucose = baseline (exercise start time) glucose – end of exercise glucose *

* Note: If the exercise was stopped early because of hypoglycemia, then the last exercise glucose value was used for analysis (210).

In all conditions, basal insulin was returned to the usual rate immediately post-exercise. Participants rested for 30 minutes post-exercise, and then consumed a standardized meal. Meals were kept consistent within each participant; however, differed slightly between participants depending on food allergies and/or dietary restrictions (i.e. lactose intolerant, vegan, vegetarian). Meal composition consisted of ~30-50g of carbohydrates, ~10-20g of protein, and ~5-15g of fat (Lean Cuisine, Nestlé, CA). The amount of bolus insulin administered at the post-exercise meal was based on the carbohydrate content of the meal and the patient's own individualized insulin to carbohydrate ratio, insulin sensitivity index, and glycemic targets pre-programmed into their PDM. Bolus insulin was reduced by 25% of the total dose to account for the increase in insulin sensitivity post-exercise (211). If an insulin correction was suggested based on the patient's PDM settings (i.e. usual care), the full correction dose was given. Bolus insulin was administered ~10 minutes before meal consumption. Following the meal, capillary glucose was measured every 30 minutes for a total of 90 minutes before participants were sent home.

All participants were asked to consume a small, standardized snack (Glucerna® bar, 20g carbohydrates, 3g fibre, 10g protein; Abbott Laboratories, Abbott Park, IL) before bedtime with their usual bolus insulin, and set a 20% BRR for six hours to reduce the likelihood of post-exercise nocturnal hypoglycemia (13).

Laboratory Assays

Plasma samples were collected with additional capillary blood just before exercise onset, 30 minutes into exercise, immediately before meal consumption, and 90 minutes post-meal and later used to measure circulating free insulin concentrations (Crystal Chem Insulin ELISA, Elk Grove Village, IL) as per manufacturer's recommendations. In an attempt to remove antibody-bound insulin, polyethylene glycol 6000 (PEG, BioShop, ON, Canada) was used to create a PEG

precipitate (modified from Nakagawa et al. (212)). A total of 50 μL of 25 percent aqueous PEG and phosphate buffer solution (pH 7.4) was added to 50 μL of each sample and lightly spun with a Vortex mixer (Vortex-Genie® 2, Scientific Industries, Inc., NY) for 10 seconds. Samples were then centrifuged at 10,000 x g for 5 minutes and the supernatant was extracted and analyzed for circulating free insulin concentration.

Statistics

Statistical significance was set *a priori* $P<0.05$ unless otherwise indicated and a Tukey's post-hoc test was used if significant interactions were found. All statistical analyses were conducted using GraphPad Prism Version 7.0 (GraphPad Software, CA). The changes in glucose concentration, carbohydrate and fat oxidation rates, and respiratory exchange ratio from the first to the last bout of exercise were compared using two-way repeated measures ANOVA. A one-way repeated measures ANOVA was used to compare each of the following: baseline glucose, change in blood glucose, nadir glucose, decremental area under the curve (AUC), and mealtime bolus insulin across all three conditions. The median and interquartile range (IQR) were used to report age, duration of diabetes, MET-min/week, absolute and relative VO_2, heart rate, fat and carbohydrate oxidation rates, blood glucose at exercise onset, change in blood glucose from the start of exercise, area under the curve, nadir glucose, time to first hypoglycemic event, amount of carbohydrate intake for the hypoglycemia rescue, mealtime bolus insulin, and overnight CGM recovery data. Significant differences in the percent time in euglycemia (70-180 mg/dL), hyperglycemia (>180 mg/dL), and hypoglycemia (<70 mg/dL) were compared using a nonparametric Friedman test.

Results

A total of 17 participants (4 male, 13 female) were recruited for this study. Participants were all adults (age 31 ± 10 [28; 25–35] years; mean ± SD [median; IQR]), with a BMI of 25.3 ± 2.5 kg/m^2, and HbA_{1c} of 6.5 ± 0.5 % (47 ± 5 mmol/mol). The total daily insulin dose was 31 ± 8 units (0.43 ± 0.1 U/kg) and diabetes duration was 14 ± 10 (10; 5–21) years. Based on two questionnaires used to assess hypoglycemia awareness (Gold score = 3 ± 1 and Clarke score), five participants had reduced hypoglycemia awareness and 12 were hypoglycemia aware. Based on the IPAQ-SF, participants were moderate to highly active (MET-mins/week = 2,805 ± 1,365 [2,782; 1,937–3,746]), as such the participant group could be categorized as active, but not highly fit based on BMI or VO_2peak (41.6 ± 5.9 mL·kg·min^{-1}).

The cardiometabolic and glycemic outcome variables are all shown in Table 1. The relative exercise intensity across all three experimental conditions was 50.3 ± 3.3% of VO_2peak and heart rate was 123 ± 12 beats per minute. The respiratory exchange ratio values did not differ significantly across the three conditions (P > 0.05). In the 80% and 50% BRR arms, carbohydrate oxidation rates tended to decrease from the start to end of exercise (both, P = 0.06), but remained constant during pump suspension (P = 0.45). Fat oxidation rates did not change from the start to end of exercise across any of the conditions (P > 0.05).

Figure 5.1A represents the absolute glucose concentrations from pre-exercise until the end of the meal challenge across all three conditions. Prior to exercise start (minus 10 minutes), blood glucose was higher in 50% BRR compared to 80% BRR (P < 0.001). Blood glucose at exercise onset (denoted as t = 0) was also significantly higher in 50% BRR compared to the other two conditions (Figure 5.1A, Table 5.1, both P < 0.001). From 10 minutes pre-exercise until the end of the meal challenge, glucose concentration was higher in 50% BRR compared to pump

suspension (all $P < 0.001$). From 30 minutes into exercise until 90 minutes into the meal challenge, blood glucose was also higher for 80% BRR versus pump suspension ($P < 0.01$). During the meal challenge, blood glucose concentration tended to be lower in pump suspension as compared to the two other arms ($P < 0.01$; Figure 5.1A). However, the greatest rise in glycemia was apparent in pump suspension as compared to the other two other arms ($P < 0.001$). Blood glucose rose at mealtime in pump suspension and in 50% BRR (both $P < 0.001$), but failed to rise significantly in the 80% BRR arm ($P = 0.16$). The mean ± SD (median; IQR) mealtime bolus insulin was 2.9 ± 1.1 (2.6; 2.2–3.5) U (80% BRR), 3.1 ± 1.2 (3.8; 1.9–3.9) U (50% BRR), and 2.6 ± 1.1 (2.3; 1.7–3.5) U (pump suspension) (not significantly different, Table 5.1).

Figure 5.1B shows the change in blood glucose concentration from 30 minutes pre-exercise to 90 minutes post-meal challenge, normalized to starting exercise glucose level. There was a significant trial by time interaction for the change in blood glucose during exercise ($P < 0.001$). Specifically, the change in blood glucose from the start to end of exercise was -31 ± 58, -47 ± 50, and -67 ± 41 mg/dL in 80% BRR, 50% BRR, and pump suspension conditions, respectively ($P = 0.008$). The decremental AUC was greatest in pump suspension compared to 80% BRR ($P = 0.007$). Also, nadir blood glucose during exercise was lower in pump suspension versus 50% BRR ($P = 0.02$). The highest number of hypoglycemic events occurred during pump suspension (n = 7/17, 41%) compared to 50% and 80% BRR (both n = 1/17, 6%, $P < 0.02$, Chi-square). If hypoglycemia occurred during exercise, the average carbohydrate intake required to return blood glucose to target range was 19 ± 6 grams (16; 16–16 grams) and the average time before resuming exercise was 19 ± 4 minutes (17; 16–21 minutes). The time to the first

hypoglycemic event ranged between 29-51 minutes during exercise in the nine hypoglycemic events that occurred during the 51 total exercise sessions.

Figure 5.2 represents circulating free insulin concentrations across all conditions. At exercise start, circulating free insulin concentration was higher in pump suspension compared to 80% BRR ($P = 0.02$) and 50% BRR ($P = 0.04$). Insulin concentration fell during exercise in all conditions ($P = 0.01$, main effect of time). However, there was no significant difference in insulin concentration among the three treatment arms by the end of the meal challenge. In examining the pre- and post-meal insulin levels specifically, we observed a rise in insulin concentrations in 82% of all cases (if all treatment conditions are combined). However, we noted a drop in insulin in the other 18% of cases. The mean plasma insulin concentration pre-meal was 67 pmol/L increasing to 94 pmol/L (i.e. 52% increase, $P = 0.02$). It may be that the variability in insulin levels and/or the noise of the insulin assay limited our ability to observe the expected rise in insulin concentrations 90 minutes following meal ingestion.

Figure 5.3A represents interstitial glucose from 10:00PM-7:00AM post-exercise across all conditions. Interstitial glucose remained relatively stable overnight with no difference across any of the three conditions ($P > 0.05$). The mean ± SEM (median, IQR) for glucose levels overnight was 131 ± 12 (122, 97–152) mg/dL, 136 ± 10 (131, 103–160) mg/dL, and 140 ± 13 (135, 105–169) mg/dL in 80% BRR, 50% BRR, and pump suspension conditions, respectively ($P > 0.05$). Figure 5.3B represents the mean percentage of time in euglycemia (70-180 mg/dL), hyperglycemia (> 180 mg/dL), and hypoglycemia (< 70 mg/dL). The percent time in the euglycemia range (mean ± SEM) for 80% BRR was 83 ± 7%, for 50% BRR was 83 ± 6%, and for pump suspension was 78 ± 8% (not significantly different; $P = 0.8$). The time spent in hyperglycemia was similar across all treatment arms at 15 ± 7%, 16 ± 6%, and 17 ± 8% for the

80% BRR, 50% BRR, and pump suspension arms, respectively (P = 0.9). The time spent in hypoglycemia was slightly higher with pump suspension (5 ± 3%), compared to the other two arms (2 ± 2% and 1 ± 1% for the 80% BRR and 50% BRR, respectively), but was not significant (P = 0.4).

Discussion

Regular physical activity is at the cornerstone of care for people living with type 1 diabetes for a number of health and fitness reasons (13). However, maintaining reasonable glucose control for prolonged moderate-intensity aerobic activities remains a major challenge, even for patients on CSII therapy (182). If prolonged exercise is to be performed soon after a meal, then bolus dose reductions by 25-75%, depending on the intensity and duration of the activity help limit hypoglycemia (123). However, if the activity is three or more hours after a meal with bolus insulin, then a BRR may be a more appropriate approach for those using CSII (13). Previous studies have shown that even with pump disconnect (115, 116), or with a temporary BRR (by 50-80%) set up to 40 minutes before exercise (84, 117), hypoglycemia remains a concern during aerobic exercise. Although recent guidelines recommend a BRR set 60-90 minutes pre-exercise for patients with type 1 diabetes on CSII (13, 14, 78, 203), we know of only one study published to date that has examined the efficacy of a 50% BRR set 60 minute pre-exercise until 60 minutes post-exercise (84). Therefore, the aim of the present study was to determine the efficacy of three different BRR strategies (one for spontaneous exercise, two for pre-planned exercise) on attenuating the drop in glycemia during and after prolonged aerobic exercise in adults with type 1 diabetes on CSII.

Roy-Fleming et al. (117) recently published that an 80% BRR up to 40 minutes pre-exercise is insufficient to reduce hypoglycemia during a 45-minute bout of submaximal aerobic

exercise. One of the main differences in our study was that the BRR was set much earlier (i.e. 90 minutes pre-exercise) in an attempt to lower circulating insulin before exercise onset. We show that 50-80% BRR set 90 minutes before prolonged aerobic exercise better protects against hypoglycemia than pump suspension at exercise onset, likely because this forecast strategy results in lower circulating insulin levels at the start of exercise as compared to pump suspension at exercise onset. In the pump suspension condition at exercise onset, 7/17 (41%) participants experienced hypoglycemia during exercise, whereas only 1/17 (6%) experienced hypoglycemia in both 80% BRR and 50% BRR ($P < 0.05$). Pump suspension at exercise onset helps with attenuating the drop in blood glucose concentration as compared to leaving the pump at the usual basal rate (i.e. 100%) (176), but this approach is clearly not sufficient to eliminate hypoglycemia risk if patients initiate exercise with a normal or only slightly elevated blood glucose level, as seen in our study (i.e. 41% of subjects developed hypoglycemia with pump suspension).

It is important to note, however, that a more aggressive approach (i.e. 50-80% BRR set 90 minutes pre-exercise) may eliminate the risk of hypoglycemia, but may also cause some patients to have elevated blood glucose at exercise onset or contribute to rebound hyperglycemia post-exercise (13). However, we found that 50-80% BRR did not lead to overt hyperglycemia before the onset of exercise nor did it result in hyperglycemia in early recovery. Interestingly, for unknown reasons, 50% BRR resulted in a higher starting blood glucose level as compared to 80% BRR and pump suspension. Moreover, from the start to end of the meal challenge, the greatest rise in glycemia was observed in pump suspension and 50% BRR. Pump suspension causing the largest rise in glycemia is likely attributable to the 7/17 participants that were treated for hypoglycemia during exercise. Thus, treating hypoglycemia during exercise with a carbohydrate snack (~15-20 g), while essential for safety reasons, may compromise glucose

tolerance at the upcoming meal. Interestingly in Figure 5.1A-B, blood glucose returned near the baseline pre-exercise glucose level in all conditions and 80% BRR did not compromise glycemia during the meal challenge. Thus, exercise before a meal, even with a BRR, appears to be associated with a very modest glycemic excursion at the meal following exercise. It should also be mentioned that overall glucose control during the meal challenge was not different among the three treatment strategies and that all approaches resulted in excellent overall glucose control in the evening post-exercise (Figure 5.3A-B).

At the onset of exercise, lower circulating free insulin concentrations were apparent in the 80% and 50% BRR, both set 90 minutes pre-exercise, as compared to pump suspension at exercise onset. Circulating free insulin continued to decline across all conditions from the start to end of exercise, thereby demonstrating that all strategies appear to lower circulating insulin levels during exercise. Previous literature has shown a modest short-term exercise-related increase in circulating insulin, followed by an accelerated decline in concentrations as the exercise continues (83, 84). However, we did not find this initial rise in insulin level during the first 30 minutes of exercise, possibly because not enough earlier time points were examined to profile the true kinetic changes in insulin levels in our study. Interestingly, circulating free insulin levels did not rise markedly at mealtime in our study (Figure 5.2), although a majority of subject participants did have a small rise in circulating insulin levels. The failure to observe a meal-related rise in circulating insulin levels may have been because of the prolonged reduction in basal insulin infusion before the meal (lasting up to 165 minutes) and the relatively small dose of insulin that was administered at mealtime (the meal bolus was reduced by 25% to account for increased insulin sensitivity post-exercise).

Importantly, and for the first time, we show that a 50-80% BRR set 90 minutes before prolonged aerobic exercise does not cause overt hyperglycemia pre-exercise, and also attenuates the drop in glycemia during aerobic exercise. However, we also acknowledge that no singular approach is likely to work for all individuals. Specifically, Supplemental Figure 5.4 shows the individual and the mean participant change in glycemia during exercise in each of the three BRR strategies. As can be observed, one participant developed hypoglycemia in all three conditions, some developed a significant rise in glucose, and some tended to have minimal glucose excursions. Thus, BRR strategies attenuate the drop in glycemia during prolonged aerobic exercise, but may still need to be individualized for any given patient.

This study had a number of strengths including random crossover design, standardization of the meal and snack following exercise, and the measurement of circulating free insulin. However, this study also had a number of limitations that need to be mentioned. There are multiple factors that may limit our ability to translate the present findings across a wider type 1 diabetes population. For example, the participants enrolled in this study were primarily female, with very good HbA_{1c} (6.5 ± 0.5 % or 47 ± 5 mmol/mol) as determined using a point-of-care device and all participants were using Omnipod® Insulin Management System (Insulet, Billerica, MA) CSII therapy. In addition, we did not have information on potential lipodystrophy and lipohypertrophy and we did not do a run-in period to assess participants' usual basal insulin rates prior to study enrolment. We also only examined exercise at one time of day (late afternoon) and with one type and intensity of exercise (prolonged moderate intensity walking/light jogging). Finally, we failed to examine if other factors, such as menstrual phase, fitness, or disease duration influenced our findings. Future studies should examine if these results translate to a larger patient population.

In conclusion, we found that a 50-80% BRR performed 90 minutes before the onset of prolonged aerobic exercise optimizes open-loop glucose control and decreases hypoglycemia risk during exercise while not compromising the post-exercise meal glucose control in patients living with type 1 diabetes. These findings support recent guidelines that pre-planned BRR well in advance of prolonged exercise is an effective strategy to reduce hypoglycemia risk and minimize the need for carbohydrate feeding during the activity (13). Whether the type 1 diabetes community can adopt this pre-planning strategy effectively still needs to be determined.

Acknowledgements: The authors would like to thank all of the participants for their time and dedication to the study. Thank you to Dr. Julian Aiken and Trevor Teich for their technical expertise and assistance with the insulin ELISA kits.

Duality of Interest: This study was funded by Insulet Canada and Insulet Corporation, USA. DPZ has received speaker's honoraria from Medtronic Diabetes and Ascensia Diabetes. MCR has received speaker's honoraria from Medtronic Diabetes, Insulet Corporation, Ascensia Diabetes, Novo Nordisk (via JDRF PEAK Program), Xeris Pharmaceuticals, Lilly Diabetes, and Lilly Innovation. TV and TL are both employees and shareholders of Insulet Corporation. No other potential conflicts of interest relevant to this article were reported.

Author Contributions: DPZ and MCR designed the study and wrote the manuscript; DPZ was responsible for data collection, interpretation of data, and analysis. SM and RP assisted in the data collection. All authors contributed feedback and revisions for the final manuscript. Dr. Michael Riddell is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation: Parts of this study were presented during the oral session entitled "Effects of Exercise on Metabolic Health in Type 1 and Type 2 Diabetes" at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

TABLES & FIGURES

	80% BRR (At t = -90 mins)		50% BRR (At t = -90 mins)		Pump Suspension (At t = 0 mins)	
Absolute VO_2 (L/min)	20.7 ± 3.33 *20.1 (18.6-22.6)*		21.1 ± 3.63 *21.2 (18.8-22.8)*		21.0 ± 3.33 *20.9 (19.9-22.6)*	
Relative VO_2 (%)	49.8 ± 3.11 *49.1 (47.7-52.6)*		50.7 ± 3.89 *49.4 (47.9-53.9)*		50.5 ± 3.04 *50.7 (48.7-52.4)*	
Heart rate (bpm)	122 ± 11 *124 (118-130)*		124 ± 12 *130 (116-133)*		124 ± 13 *126 (118-133)*	
EXERCISE TIME	**10-15 mins**	**55-60 mins**	**10-15 mins**	**55-60 mins**	**10-15 mins**	**55-60 mins**
Respiratory exchange ratio	0.87 ± 0.04 *0.9 (0.8-0.9)*	0.86 ± 0.05 *0.9 (0.8-0.9)*	0.87 ± 0.05 *0.9 (0.8-0.9)*	0.86 ± 0.03 *0.9 (0.8-0.9)*	0.87 ± 0.05 *0.8 (0.8-0.9)*	0.88 ± 0.06 *0.9 (0.8-0.9)*
Carbohydrate oxidation (g/min)	2.06 ± 0.6 *1.9 (1.8-2.4)*	1.87 ± 0.5 *1.8 (1.6-2.1)*	2.15 ± 0.7 *2.1 (1.8-2.4)*	1.91 ± 0.5 *1.9 (1.7-2.0)*	1.84 ± 0.6 *1.7 (1.4-2.1)*	1.82 ± 0.7 *1.7 (1.5-1.8)*
Fat oxidation (g/min)	0.29 ± 0.1 *0.3 (0.2-0.4)*	0.32 ± 0.2 *0.3 (0.2-0.4)*	0.31 ± 0.1 *0.3 (0.2-0.4)*	0.32 ± 0.1 *0.3 (0.3-0.4)*	0.34 ± 0.2 *0.3 (0.3-0.4)*	0.31 ± 0.2 *0.3 (0.2-0.4)*
Blood glucose (mg/dL) **at exercise start**	164 ± 41 *157 (133-171)*		191 ± 49 * *184 (153-221)*		164 ± 45 *157 (142-180)*	
Δ **glucose** (mg/dL) **from start-end of exercise**	-31 ± 58 *-32 (-74 to 11)*		-47 ± 50 *-45 (-88 to -14)*		-67 ± 41 * *-65 (-90 to -38)*	
Decremental area under curve (AUC)	-64 ± 110 *-86 (-141 to 20)*		-89 ± 99 *-86 (-143 to -6)*		-142 ± 81 * *-136 (-186 to -79)*	
Nadir glucose (mg/dL) **during exercise**	122 ± 47 *112 (86-146)*		137 ± 50 *148 (95-148)*		97 ± 45 * *88 (67-103)*	
Time to first hypoglycemic event (mins)	45		30		40 ± 11 *45 (30-45)*	
Number of hypoglycemic events	1		1		7 *	
Mealtime bolus insulin (units)	2.9 ± 1.1 *2.6 (2.2-3.5)*		3.1 ± 1.2 *3.8 (1.9-3.9)*		2.6 ± 1.1 *2.3 (1.7-3.5)*	

Table 5.1: Cardiometabolic and glycemic outcome variables.
Data represented as mean ± SD or *median (IQR)*, n=17. **Note:** 10-15 mins and 55-60 mins refer to the last 5 minutes of the beginning and end of exercise where metabolic data was collected. * indicates significantly different from the other two treatment arms ($P < 0.05$).

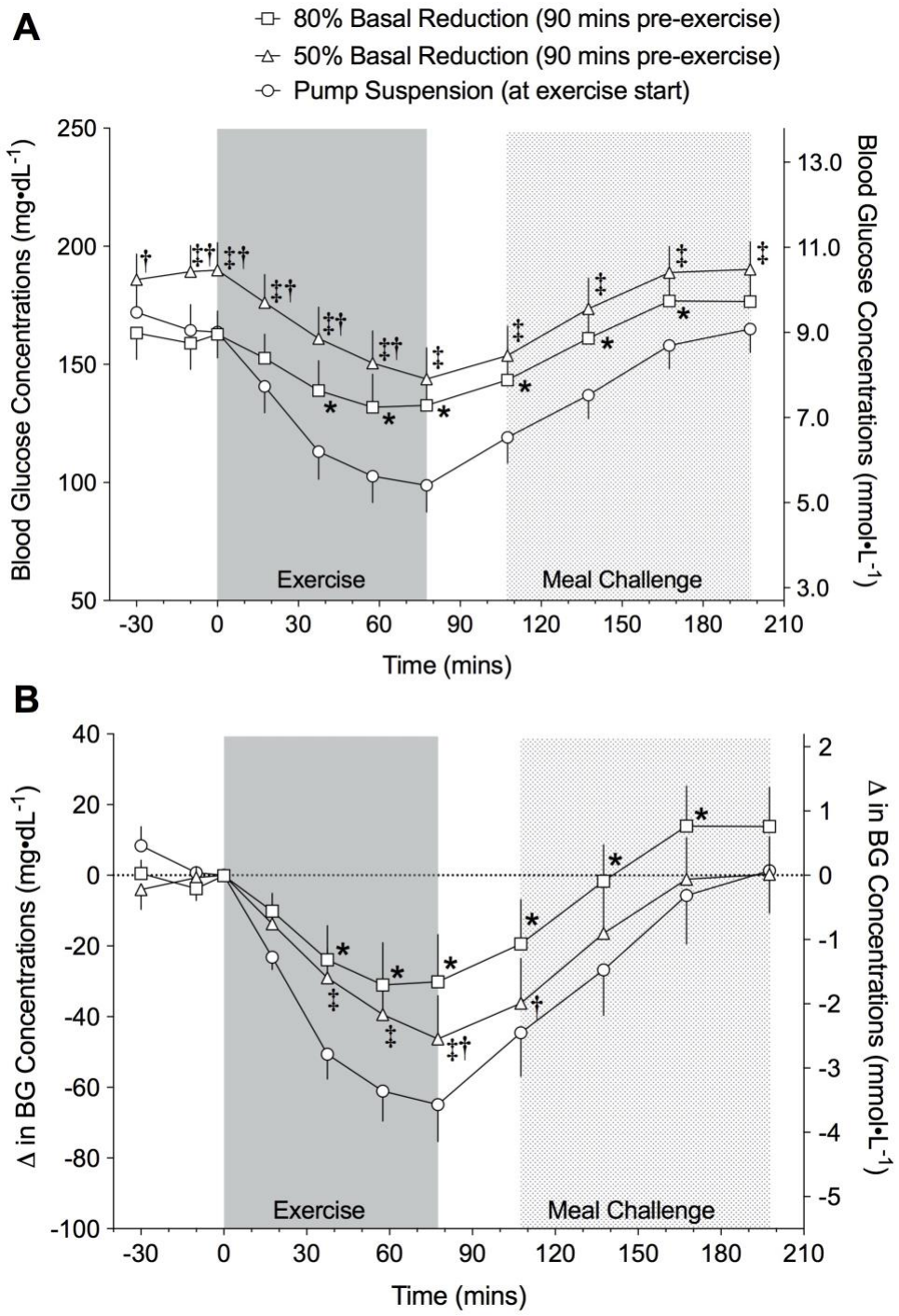


Figure 5.1: Absolute and relative change in blood glucose level.

A, absolute blood glucose concentration during exercise and meal challenge across all treatment arms. B, relative change in blood glucose concentration during exercise and meal challenge across all treatment arms. * represents 80% BRR vs. pump suspension. † represents 50% BRR vs. 80% BRR. ‡ represents 50% BRR vs. pump suspension. Data represents mean ± SEM.

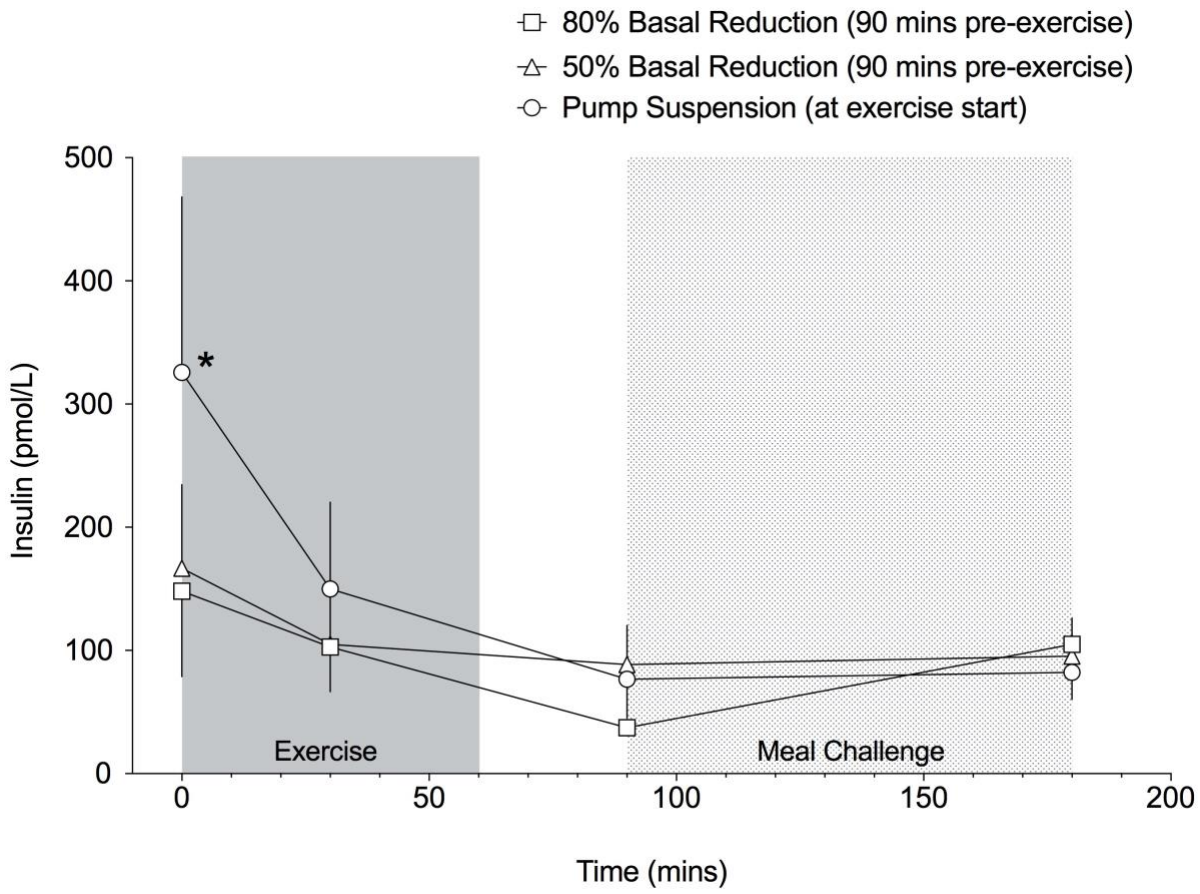


Figure 5.2: Circulating free insulin concentrations.

Circulating insulin concentrations from the start to the end of exercise across all treatment arms. * represents pump suspension vs. both 50% BRR and 80% BRR. Data represents mean ± SEM.

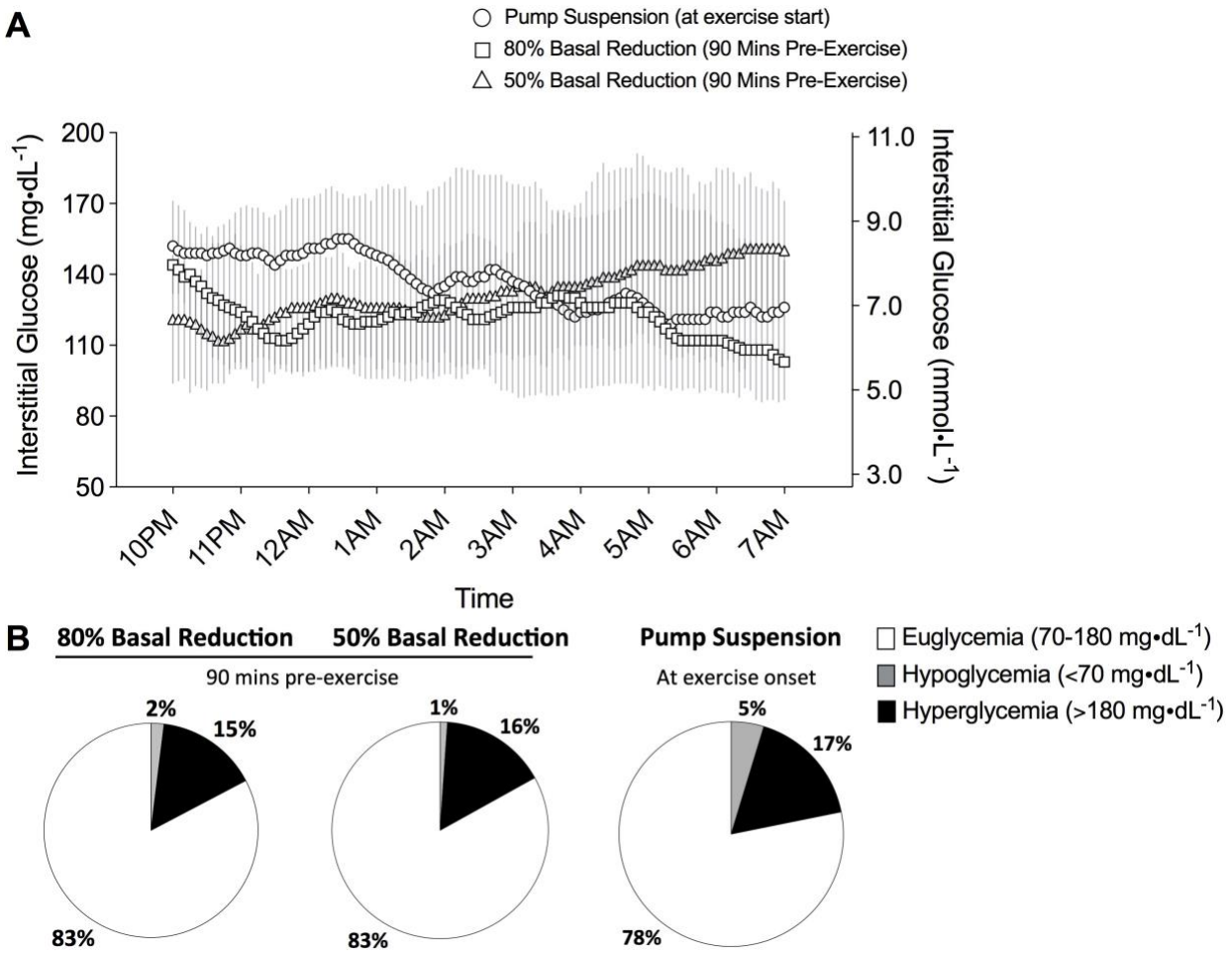
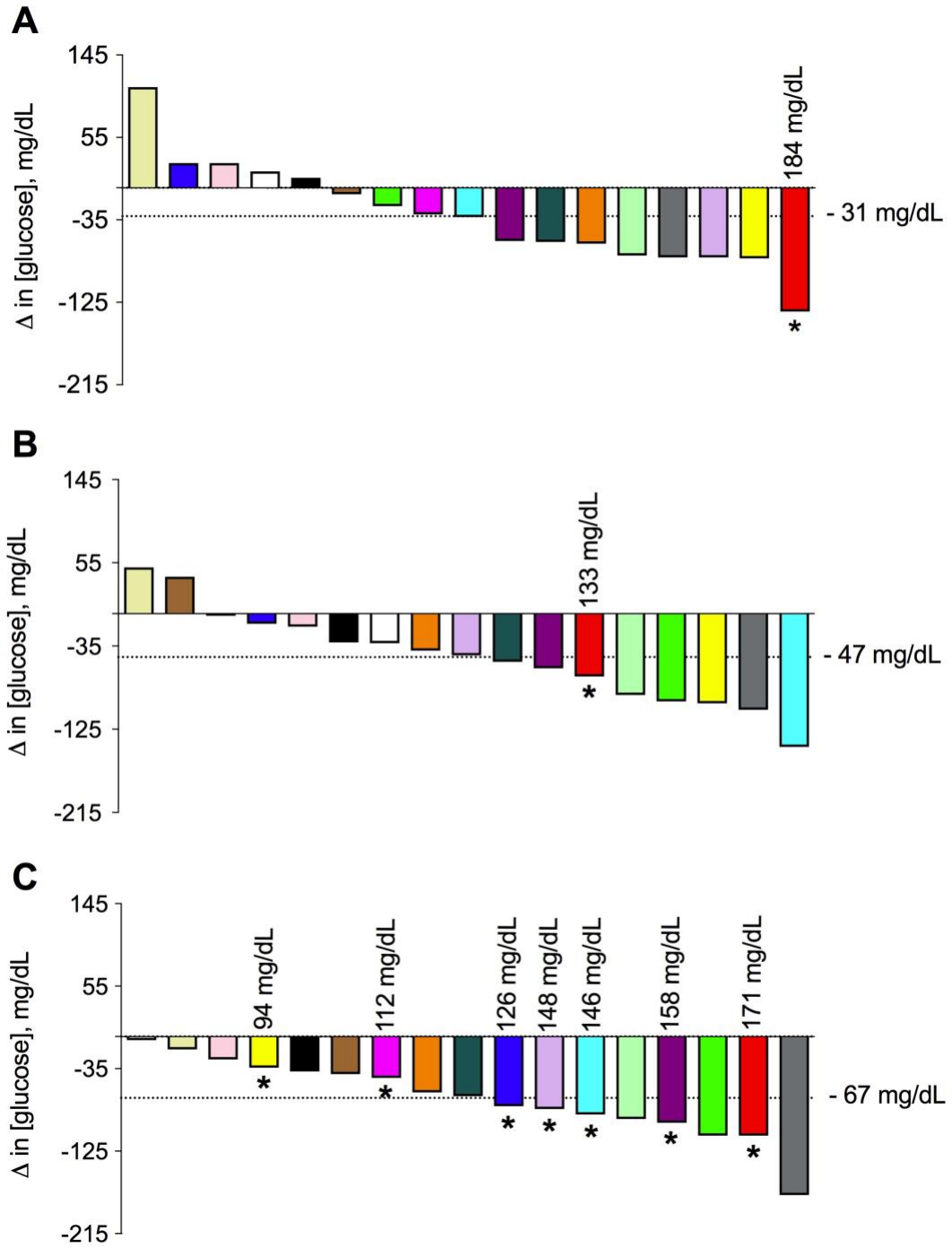


Figure 5.3: Interstitial glucose and percent time in range.

A, Overnight recovery CGM glucose data from 10:00PM – 7:00AM across all treatment arms. Data represent median and IQR. B, Percent time spent in euglycemia, hyperglycemia, and hypoglycemia (n = 15). Data represents mean ± SEM. CGM, continuous glucose monitor.



Supplemental Figure 5.4: Individual and mean change in glucose concentration.

A, 80% BRR; B, 50% BRR; and C, pump suspension. * denotes hypoglycemia developed (< 70 mg/dL) during exercise. Colour coding used to differentiate between participants and carried out between treatment arms. Baseline blood glucose concentration denoted above each subject that experienced hypoglycemia during exercise (mg/dL).

6.0 ACADEMIC PAPER 4

Lag time remains with newer real-time continuous glucose monitoring technology during aerobic exercise in adults living with type 1 diabetes

Under Review in Diabetes Technology, and Therapeutics, 2018

Lag time remains with newer real-time continuous glucose monitoring technology during aerobic exercise in adults living with type 1 diabetes

Short Title: Continuous glucose monitoring lag during exercise

Dessi P. Zaharieva (M.Sc.)*[1], Sarah McGaugh (B.Sc.)[1], Rubin Pooni (B.Sc.)[1], Todd Vienneau (B.Sc.)[2], Trang Ly (MBBS, FRACP, Ph.D.)[3], & Michael C. Riddell (Ph.D.) [1, 4]

[1] – Department of Kinesiology & Health Science, Faculty of Health, Muscle Health Research Centre, York University, Toronto, ON, Canada

[2] – Insulet Canada Corporation, Oakville, ON, Canada

[3] – Insulet Corporation, Billerica, Massachusetts, USA

[4] – LMC Diabetes & Endocrinology, Toronto, ON, Canada

Correspondence to:

Dr. Michael Riddell, Ph.D.

School of Kinesiology and Health Science

York University

4700 Keele Street, Toronto, ON, M3J 1P3

Keywords: Continuous Glucose Monitoring, Accuracy, Exercise, Sensors, Self-monitoring of blood glucose, Time Lag

Abstract

Background: Real-time continuous glucose monitor (rtCGM) devices track glucose levels in the interstitial fluid and help detect glycemic excursions associated with exercise, meals, and insulin dosing in patients with type 1 diabetes. However, the delay in equilibrium between interstitial and blood glucose levels during exercise and meals may result in rtCGM underestimating the true change in glycemia during activity and post exercise feeding. The purpose of this study was to examine rtCGM discrepancies during continuous steady state moderate intensity aerobic exercise and the meal post exercise as compared to two commonly used self-monitoring of blood glucose (SMBG) devices.

Methods: A total of 17 adults (13 female, 4 male) with type 1 diabetes using insulin pump therapy (OmniPod®, Insulet, USA) and rtCGM (Dexcom®, USA) completed 60 min of exercise on three occasions. A standardized meal was given 30 min post-exercise. Blood glucose levels were measured during exercise and meal recovery using two SMBG devices: glucose meter 1 (Contour® Next Link; Ascensia Diabetes Care, USA); and b) glucose meter 2, [Omnipod® Personal Diabetes Manager; (PDM) with built-in glucose meter (FreeStyle, Abbott Laboratories, USA)], while rtCGM was measured with a third device [either Dexcom G4® (n=4) or G5® (n=13)], which was calibrated with the subjects' PDM.

Results: Glucose meter 1 values were higher than glucose meter 2 and rtCGM across all time points during exercise and meal challenge (both $P<0.05$). Because of this initial bias and since rtCGM was calibrated to glucose meter 2, all devices were normalized to the baseline glucose concentration. SMBG devices showed a similar decline in blood glucose during exercise and similar rise during mealtime, while the rtCGM time delay was ~10-15 mins. Mean absolute relative difference (MARD) values for rtCGM as compared to glucose meter 1 were 12±9%,

11±9%, and 14±11% during rest, exercise, and meal, respectively (P=0.06). Similarly, MARD values for rtCGM as compared to glucose meter 2 were 11±9%, 17±14%, and 11±10% during rest, exercise, and meal, respectively (P=0.001). Based on Clarke Error Grid analyses, rtCGM values were in zones A and B 99-100% of the time relative to glucose meter 1 and 94-99% of the time for glucose meter 2 (P>0.05).

Conclusion: In summary, rtCGM values underestimate the drop in glycemia during exercise and appear to lag behind blood glucose values by ~10-15 mins when glucose levels are rapidly changing. Therefore, if hypoglycemia is suspected during exercise, individuals should confirm glucose levels with a fingerstick capillary glucose measurement.

Introduction

A real-time continuous glucose monitor (rtCGM) consists of a wearable subcutaneous sensor containing an electrode used to automatically measure interstitial glucose approximately every 5 minutes and a transmitter that sends these readings to an insulin pump, mobile device, or remote receiver (7). The sensor relies on glucose molecules in the interstitial fluid that initiate the release of electrons on the electrode (7). These electrons generate a current that is proportional to the glucose level and the current is relayed to a transmitter that is attached to the sensor. Glucose-monitoring devices have been shown to detect greater glucose variability (42), rate of change in glucose concentration, and incidence of hypoglycemia compared to self-monitoring of blood glucose (SMBG) using a traditional glucose meter, a lancing device, and capillary blood sampling (213). Since rtCGM systems can provide insight into glucose patterns and overall diabetes management, these devices have recently been included in the clinical guidelines and standards of care for individuals with diabetes, particularly if they are dosing insulin (146, 214).

One common measure of rtCGM accuracy is mean absolute relative difference (MARD), which is the mean absolute difference between the reference (often SMBG) and interstitial glucose divided by the reference. Successive generations of devices have improved accuracy with a lower MARD when comparing to the laboratory standards (Yellow Springs Instruments [YSI] glucose analyzer) for plasma glucose measurements leading to non-adjunctive status, so that insulin dosing and decision-making around hypoglycemia treatment can be made using some of these devices (214-216). Kovatchev et al. (217) reported that using rtCGM for insulin dosing decisions is feasible at a MARD of 10% or lower. Whether MARD remains stable in rtCGM throughout dynamic changes in glucose (often associated with exercise and meal ingestion) is unclear.

In an earlier field study (79), rtCGM was shown to help guide patients on when to initiate carbohydrate feeding during physical activity in active adolescents and young adults with type 1 diabetes. However, that study did not determine if the sensor glucose was an accurate reflection of the SMBG during physical activity. More recently, CGM devices have been heavily scrutinized in the context of exercise due to the apparent lag in equilibrium between interstitial and blood glucose (165, 167, 189, 218). This lag is often attributed to: a) physiologic lag affected by blood flow (165); b) sensor reaction time to glucose (219); and c) signal processing (163). These discrepancies between rtCGM devices and SMBG may impact insulin-dosing decisions and carbohydrate replacement, particularly around exercise and during meals when glucose levels can change rapidly. In line with this, Biagi and colleagues (220) reported an increase in MARD from 9.5% to 16.5% during aerobic exercise. Interestingly, Adolfsson et al. (221) reported that MARD values tended to increase with vigorous-to-maximal intensity exercise (e.g. football, cross-country skiing) compared to low-to-moderate intensity activities (e.g. golf) in adolescents with type 1 diabetes. However, this has not been consistently observed in studies examining intermittent high intensity exercise (190, 191), likely because glucose levels tend not to change as dramatically because of a rise in glucose counterregulatory hormones and lactate levels (13).

The primary purpose of this study was to assess the accuracy of newer rtCGM technology compared to SMBG using two different blood glucose meters during prolonged, continuous steady state moderate-intensity ‘aerobic’ exercise and the meal post-exercise in adults living with type 1 diabetes. Our hypothesis is that rtCGM accuracy and MARD values will deteriorate during prolonged, aerobic exercise and during the meal challenge post exercise.

Methods

Study Participants

The present study conformed to the standards set by the Declaration of Helsinki and was approved by the Research Ethics Board at York University. The study was registered at clinicaltrials.gov in 2017 (identifier: NCT03130101). This is ancillary data from a previously published study (122) and we used the rtCGM data for a secondary analysis here. A total of 17 individuals (4 male, 13 female) with type 1 diabetes were recruited for the study. The inclusion criteria included 17-65 years of age, duration of diabetes > one year; using insulin pump treatment (Omnipod® Insulin Management System, Insulet, Billerica, MA) for at least one month; a total daily insulin dose of at least 0.25 units/kg; and $HbA_{1c} \leq 9.9\%$ (85 mmol/mol). The exclusion criteria included unpredictable hypoglycemia; unable to perform regular exercise due to injury; having conditions that may make exercise unsafe (i.e. high blood pressure, late pregnancy, etc.); and/or physician diagnosis of active diabetic retinopathy or neuropathy. Written informed consent was obtained from all participants prior to study initiation.

Experimental Design

All exercise testing took place at York University in the Clinical Human Exercise Laboratory. Participants took part in one preliminary visit and three experimental visits in which aerobic exercise was performed with different basal insulin rate settings to help mitigate the risk for hypoglycemia (122). The preliminary testing consisted of completing a consent form, questionnaires, anthropometric measurements, and a peak oxygen consumption (VO_2peak) test. The experimental visits included three continuous steady state moderate intensity aerobic exercise bouts with different adjustments in basal insulin, completed in a randomized, counter-balanced fashion. Participants were asked to refrain from all forms of vigorous-to-maximal

exercise (i.e. activities > six metabolic equivalents) for 24 hours prior to each visit and were asked to avoid alcohol and caffeine consumption during the monitoring period. During the experimental visits, female participants were not tested during the luteal phase, where applicable.

Preliminary Testing (Visit 1)

During the preliminary testing, height, body mass, blood pressure, body fat percentage (Tanita Scale, model TBF-612, Arlington Heights, Ill), and HbA_{1c} (A1cNow+, Roxon Medi-tech Ltd., QC) were measured. The VO_2peak test was an incremental-to-maximum treadmill protocol and was measured using a portable metabolic system (K5, COSMED, Rome, Italy) and heart rate monitor (Polar Electro, Kemple, Finland). The metabolic unit measures breath-by-breath expired oxygen and carbon dioxide concentrations using an oxygen sampling line, turbine flowmeter, harness, facemask and head strap.

Continuous Glucose Monitor

All participants were instrumented with rtCGM sensor and transmitter (Dexcom G4® or G5®, San Diego, CA) at least 24 hours prior to testing and were provided with a receiver or mobile app to track interstitial glucose levels throughout the study. A total of seven participants were trained on the operation of rtCGM and the remaining 10 participants were asked to continue using their own rtCGM throughout the study duration and to calibrate their rtCGM using their Personal Diabetes Manager (PDM) for SMBG. Of the 17 participants, four used rtCGM with Dexcom G4® Platinum with 505 algorithm (started prior to the study) and the remaining (n=13) used rtCGM with Dexcom G5® throughout the study. Participants wore rtCGM for one week at a time and were instructed to use their PDM for SMBG using the built-in glucose meter and associated blood glucose test strips (FreeStyle Lite, Abbott, Laboratories, Chicago, IL). Following an initial warm-up period of two-hours after sensor insertion, participants were

advised to calibrate at least once every 12-hours using their own PDM glucose meter. If testing was scheduled ≥ one week apart, participants were asked to insert a new sensor at least 24 hours prior to the next experimental visit. All rtCGM data was uploaded to a Healthcare Professional Dexcom Clarity® account and later retrieved for interstitial glucose analysis.

Experimental Sessions (Visits 2-4)

All participants completed three aerobic exercise visits that were separated by at least 24 hours and all sessions were pooled for this analysis. Participants were asked to consume the same lunch of their choice and take their usual mealtime bolus insulin (plus correction, if necessary) no later than 11:30AM. The three insulin adjustment strategies included a) pump suspension (100%) at exercise start, for the duration of the activity; b) a 50% basal reduction, set 90 minutes pre-exercise for the duration of the activity; and c) an 80% basal reduction, set 90 minutes pre-exercise for the duration of the activity. For the 50% and 80% reduction arms, the principal student investigator phoned each participant at 1:30PM as a reminder to reduce basal insulin for at least four hours. Exercise start time was 3:00PM for all experimental visits and consisted of 60 minutes of aerobic exercise, broken down into four 15-minute bouts with 5-minute rest periods in between. The exercise was a continuous steady state moderate-intensity (45-55% of VO_2peak) walk/light jog on a treadmill and was followed by a standardized meal challenge.

SMBG was determined at baseline/rest (i.e. 10 minutes prior to exercise and just before exercise start), every 15 minutes during exercise, and every 30 minutes during meal recovery according to good practice as described by Hortensius et al. (222). The following two blood glucose devices were used: a) *glucose meter 1* (Contour® Next Link, Ascensia Diabetes Care, Parsippany, NJ); and b) *glucose meter 2* (Omnipod® PDM; Insulet, Billerica, MA). All SMBG measurements were completed in duplicate for both meters and in triplicate if the second glucose

value differed by > 10 mg/dL from the first measurement. For analysis purposes, the average of the SMBG values were used if duplicates were performed while the average of the closest two values were used if triplicates were performed. Basal insulin rates were resumed back to the usual (100%) rate immediately following the cessation of exercise. If hypoglycemia ([blood glucose] < 70 mg/dL) developed during exercise, participants were instructed to suspend exercise and 16 grams of oral dextrose (Dex4®, AMG, QC, Canada) was provided. Following a 15-minute rest period to confirm recovery from hypoglycemia using SMBG (glucose meter 2), the exercise was resumed. After exercise, following a 30-minute period resting in a chair, all participants consumed a standardized meal containing ~30-50g of carbohydrates, ~10-20g of protein, and ~5-15g of fat (Lean Cuisine, Nestlé, CA) and blood glucose levels were monitored for 90 minutes post-meal.

Statistics

Statistical significance was set *a priori* at $P < 0.05$. All three conditions (50% BRR, 80% BRR, and pump suspension) were analyzed separately and because there were no significant differences between conditions, all data was pooled for this analysis. For absolute and change in glucose during exercise (i.e. delta from baseline), the data were pooled across the three exercise conditions. For absolute and change in glucose data, a two-way repeated measures ANOVA was conducted to compare all devices during exercise and in the meal recovery post-exercise. Data are represented as mean ± SEM. During rest, exercise, and recovery, there was no difference in Dexcom G4® and G5® glucose data when analyzed separately (data not shown), therefore all rtCGM data were pooled for all analyses. The 'rest' time points includes all 10 minute pre-exercise, exercise start, and pre-meal data. The 'exercise' time points includes 15-, 30-, 45-, and 60-minutes of exercise. The 'meal' time points include 30-, 60-, and 90-minutes following meal

ingestion. All of the graphics and statistical analyses were completed using GraphPad Prism Version 7.0 (GraphPad Software, CA). Capillary blood glucose was measured using two different glucose meter devices and each was used as the reference to evaluate the accuracy of the rtCGM. The MARD was calculated using the absolute relative difference between the glucose meter value and rtCGM value over the glucose meter value multiplied by 100. A one-way ANOVA was used to compare MARD values during rest, exercise, and meal recovery for glucose meter 1 and glucose meter 2. A paired t-test was used to compare MARD values during exercise for glucose meter 1 versus glucose meter 2.

Results

The anthropometric measurements for all 17 participants (13 females, 4 males) are summarized below. The participants recruited for this study were adults (age 31 ± 10 years; mean ± SD), on insulin pump therapy and in good metabolic control (HbA_{1c} 6.5 ± 0.5% or 48 mmol/mol).

Since blood glucose measurements were completed in duplicate for both glucose meter 1 and glucose meter 2, the coefficient of variance (CV) was calculated during rest, exercise, and meal recovery for both devices. For glucose meter 1, the CV between the first and second blood glucose reading was 1.8 ± 1.4% during rest and exercise, and 1.7 ± 1.6% during meal recovery. For glucose meter 2, the CV between the first and second blood glucose reading was 2.2 ± 1.9% during rest, 2.3 ± 2.0% during exercise, and 2.2 ± 1.7% during the meal recovery.

Figure 6.1A represents the absolute glucose concentrations as measured by all three devices during aerobic exercise and in the meal post-exercise. From 10 minutes pre-exercise to the end of meal challenge, glucose meter 1 was significantly higher than glucose meter 2 and rtCGM across all time points ($P < 0.05$). From 15 minutes into exercise until the end of exercise,

interstitial glucose was significantly higher than glucose meter 2 ($P < 0.05$). Interstitial glucose was significantly lower than glucose meter 2 from 30-60 minutes post-meal ($P < 0.05$). Because of the positive bias of glucose meter 1 as compared to the other two devices, and since rtCGM was calibrated to meter 2, the glucose data from all three devices were normalized to the pre-exercise value (at time = 0). With this data normalization, the change in glucose during exercise and meal recovery was nearly identical between the two SMBG devices (Figure 6.1B). However, from 15 minutes into exercise until the end of exercise when blood glucose was dropping, interstitial glucose was significantly higher than both glucose meters (both $P < 0.05$). In recovery, when blood glucose was rising; however, interstitial glucose was significantly lower than glucose meter 1 and glucose meter 2 at 30 minutes following meal ingestion ($P < 0.05$). At the start and end of the meal challenge, interstitial glucose was significantly higher than glucose meter 1 ($P = 0.01$).

Figure 6.2 represents the MARD values during the following time points: rest, exercise, and meal for rtCGM as compared to glucose meter 1 and glucose meter 2. The MARD value for rtCGM as compared to glucose meter 1 was 12 ± 9% during rest, 11 ± 9% during exercise, and 14 ± 11% during the meal post-exercise (Figure 6.2A, $P = 0.06$). The MARD values for rtCGM as compared to glucose meter 2 was 11 ± 9% during rest, 17 ± 14% during exercise, and 11 ± 10% during the meal post-exercise (Figure 6.2B, $P < 0.001$). The MARD values during exercise were significantly higher in glucose meter 2 as compared to glucose meter 1 ($P < 0.001$).

Figure 6.3A represents Clarke Error Grid analyses with glucose meter 1 compared to rtCGM at rest, exercise, and during the meal challenge. Based on regression analyses, the r-squared values for glucose meter 1 versus rtCGM were $r^2 = 0.84$, $r^2 = 0.85$, and $r^2 = 0.75$ during rest, exercise, and meal challenge, respectively. Similarly, Figure 6.3B represents Clarke Error

Grid analyses with glucose meter 2 versus rtCGM at rest, exercise, and during the meal challenge. Based on regression analyses, the r-squared values for glucose meter 2 versus rtCGM were similar at $r^2 = 0.82$, $r^2 = 0.82$, and $r^2 = 0.73$ during rest, exercise, and meal challenge, respectively (not significantly different from glucose meter 1, $P > 0.05$).

Table 6.1 represents the Clarke Error Grid zones A–E that are used to depict the likelihood of inappropriate treatment based rtCGM values as compared to SMBG. For glucose meter 1 as compared to rtCGM, 99% of values fell in zones A and B during rest and exercise, while 100% of values were in zones A and B during the meal challenge. For glucose meter 2 as compared to rtCGM, 99% of values fell in zones A and B during rest and the meal challenge, while 94% of values were in zones A and B during exercise.

Discussion

Previous literature has looked at rtCGM performance during both aerobic and anaerobic exercise (189-191, 220); however, to our knowledge, this is the first study to measure rtCGM accuracy during a structured 60-minute aerobic exercise bout using primarily Dexcom G5® technology (n=13). The remaining participants (n=4) wore Dexcom G4® Platinum with the updated software and 505 algorithm. In addition, our analysis showed no difference with the G4® data removed; therefore, all rtCGM data were pooled. Collectively, these more recent studies suggest that sensor accuracy, even with newer algorithms and technology, may be compromised, particularly during prolonged exercise when glucose levels tend to change rapidly (189, 191, 220, 223).

The present study assessed the accuracy of rtCGM compared to two different glucose meters during exercise and in recovery. First, we show that glucose meter 1 tended to report higher than glucose meter 2, as has been noted in other comparisons (224). Second, we found

that rtCGM had better congruence with glucose meter 2 versus glucose meter 1, likely because the rtCGM was calibrated to glucose meter 2. As such, in a real-world setting, we recommended that patients use the same glucose meter for regular SMBG and calibrations. Third, we found that after normalizing glucose values to the pre-exercise (i.e. baseline, time = 0) glucose concentration, rtCGM values underestimated the drop in glucose during exercise and lag significantly behind both meter readings by ~10-15 minutes. These findings may have critical implications for the development of hybrid closed-loop or automated insulin delivery systems for exercise since these devices may inadvertently over-deliver insulin when plasma glucose is dropping but sensor glucose fails to drop or may even rise (223). In contrast, for the meal response after exercise, the delayed rise in sensor glucose may result in insulin under-delivery as compared to plasma glucose and/or SMBG values.

A number of studies have examined the accuracy of rtCGM during exercise; some using SMBG as a reference (221), while others compare venous blood as the reference, using a glucose analyzer (190, 191, 225). The laboratory standard for CGM accuracy is most commonly a glucose analyzer (Yellow Springs Instrument, Xylem Inc., OH) (226, 227); however, we chose two commonly used SMBG meters as separate reference values in this study. In a real-world setting, patients will not have glucose analyzers available to use as a reference during exercise, and therefore, SMBG is a more realistic reference measurement. Interestingly, according to a recent study that used capillary blood glucose concentration as a reference for CGM accuracy as compared to venous blood found that SMBG as the reference was associated with significantly lower MARD values as compared to plasma glucose as measured by a glucose analyzer (HemoCue measurement system, Ängelholm, Sweden) (228).

Measuring rtCGM accuracy may be negatively impacted if the reference method is different from the method that is used to calibrate the rtCGM device (228). In the present study, all rtCGM calibrations were made using patient's own PDM glucose meter (referred to as glucose meter 2). As such, glucose meter 2 and rtCGM values were not different during rest ($P > 0.05$), but CGM lag was apparent during exercise. Although rtCGM lag was evident during exercise versus both glucose meter devices, glucose meter 1 values also started higher than rtCGM values during rest, likely because the rtCGM calibrations were made using glucose meter 2 (Figure 6.1A). As such, we normalized the data for all three devices to baseline glucose to help determine if the change in glucose was accurately reflected by rtCGM as compared to SMBG. As can be observed in Figure 6.1B, rtCGM lags behind SMBG during exercise and significantly underestimates the drop in glucose as compared to SMBG ($P < 0.001$). Unfortunately, we did not measure plasma glucose levels using a standardized glucose analyzer, so it is currently unclear which glucose meter was more accurate or if the drop in glucose as measured by rtCGM was a true underestimation of circulating plasma glucose concentrations. However, with the data that we collected, we found a low CV (%) between the first and second glucose reading for both glucose meter 1 (1.8 ± 1.5%) and glucose meter 2 (2.2 ± 1.9 %).

Despite a clear lag in interstitial glucose as measured by rtCGM during exercise, we found that sensor glucose levels had good congruency during the meal challenge. More specifically, as shown in Figure 6.3A, 100% of the values are in Zones A and B of the Clarke Error Grid during the meal challenge. It is important to recognize that the regression analysis alone does not differentiate which points are in Zones A to E. For example, the values that are in Zone D could lead to failure to detect hypoglycemia or hyperglycaemia and in Figure 6.3A during the meal, all of the points fell in safe and acceptable Zones A and B.

In summary, rtCGM technology helps patients closely monitor glucose levels and make appropriate changes in order to prevent dysglycemia. Numerous studies have reported that regular use of rtCGM lowers the time spent in hypoglycemia, and improves HbA_{1c} and quality of life in both children and adults with type 1 diabetes (229-232). However, we conclude that the accuracy of rtCGM is negatively impacted by aerobic exercise and patients need to be aware of this potential rtCGM time delay. More specifically in our study, the rtCGM lag time was ~10-15 minutes behind SMBG readings during exercise relative to two different SMBG devices. Due to this clinically important delay in interstitial glucose versus SMBG, we suggest patients increase vigilance and perform more frequent fingerstick capillary glucose monitoring around exercise. In addition, one solution to rtCGM lag as described by Turksoy and colleagues (233) includes incorporating wearable technology with automated insulin delivery which can better detect the changes in glucose levels and shows promise in the prevention of hypoglycemia during exercise. Few studies have assessed the accuracy of rtCGM and flash glucose monitor devices in patients with type 1 diabetes in outpatient settings (234, 235), therefore, future studies should also focus on comparing the newest and most advanced CGM technology in outpatient settings with a greater emphasis on exercises of varying intensities and durations.

Acknowledgements

This project was funded by Insulet Canada and Insulet Corporation, USA. The authors would like to thank all of the participants for their time and dedication to the study. Thank you to Sepehr Bozorgzadeh and Adam Weber for their assistance in graphing the Clarke Error Grids.

Contribution of Authors

DPZ and MCR designed the study. DZ was responsible for data collection, interpretation of data, and analysis. SM assisted with the MARD and Clarke Error Grid data analysis. SM and RP assisted in the data collection. All authors contributed feedback and revisions for the final manuscript. TV and TL are industry sponsors and funded the study.

Author Disclosure Statement

DPZ has received speaker's honoraria from Medtronic Diabetes and Ascensia Diabetes. MCR has received speaker's honoraria from Medtronic Diabetes, Insulet Corporation, Ascensia Diabetes, Novo Nordisk (via JDRF PEAK Program), Xeris Pharmaceuticals, Lilly Diabetes, and Lilly Innovation. TV and TL are both employees and shareholders of Insulet Corporation. No other potential conflicts of interest relevant to this article were reported.

TABLES & FIGURES

Table 6.1: Clarke Error Grid Zones

Zones	Glucose Meter 1 vs. CGM			Glucose Meter 2 vs. CGM		
	Rest	**Exercise**	**Meal**	**Rest**	**Exercise**	**Meal**
A	122/153 (80%)	164/204 (80%)	115/153 (75%)	129/153 (84%)	141/204 (69%)	127/153 (83%)
B	29/153 (19%)	38/204 (19%)	38/153 (25%)	23/153 (15%)	52/204 (25%)	25/153 (16%)
C	0/153 (0%)	0/204 (0%)	0/153 (0%)	0/153 (0%)	0/204 (0%)	0/153 (0%)
D	2/153 (1%)	2/204 (1%)	0/153 (0%)	1/153 (1%)	11/204 (5%)	1/153 (1%)
E	0/153 (0%)	0/204 (0%)	0/153 (0%)	0/153 (0%)	0/204 (0%)	0/153 (1%)

Notes: Clarke Error Grid zones A-E comparing **glucose meter 1 vs. CGM** and **glucose meter 2 vs. CGM** during rest, exercise, and meal post-exercise. Zone A = Values within 20% of glucose meter, Zone B = Points are outside of 20%, but would not lead to inappropriate treatment, Zone C = Points leading to unnecessary treatment, Zone D = Points indicate potentially dangerous failure to detect hypo- or hyperglycaemia, Zone E = Points that would confuse treatment of hypo- for hyperglycaemia and vice versa.

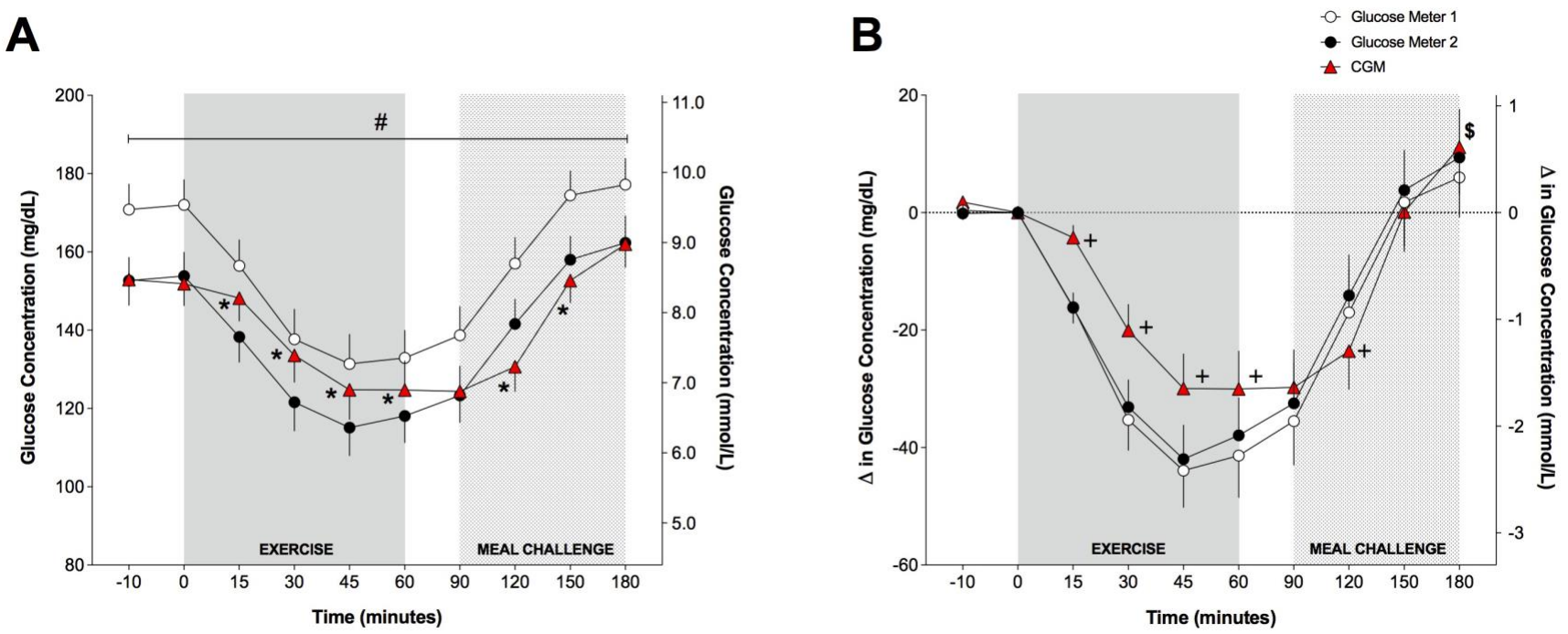


Figure 6.1: Absolute and relative change in blood glucose level.

A, Absolute values of glucose meter 1, glucose meter 2, and CGM during exercise and meal challenge. # represents glucose meter 1 different than CGM and glucose meter 2 ($P < 0.05$). * represents CGM different than glucose meter 2 ($P < 0.05$). B, Change in glucose levels (relative to time = 0) across all three devices during exercise and meal challenge. + represents CGM different than glucose meter 1 and glucose meter 2 ($P < 0.05$). **$** represents CGM different than glucose meter 1 ($P = 0.01$). Data represents mean ± SEM, n=17.

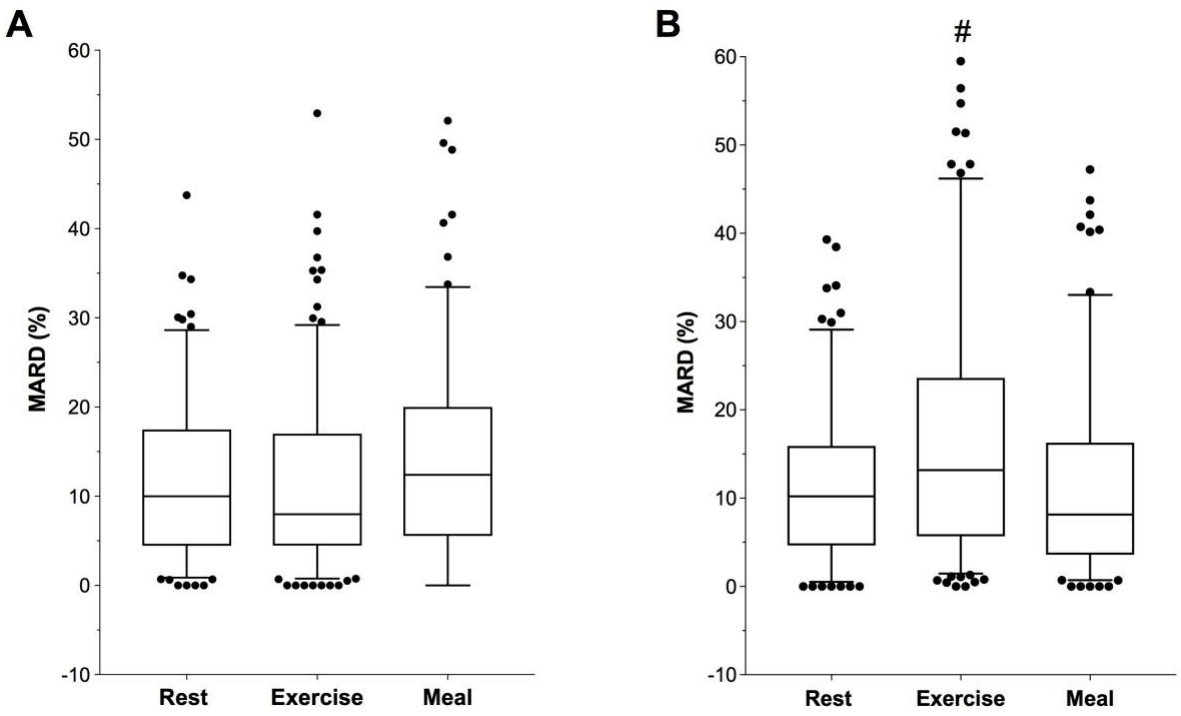


Figure 6.2: Mean absolute relative difference (%).

A, Mean absolute relative difference (MARD) comparing CGM to glucose meter 1 during rest, exercise, and meal. B, MARD comparing CGM to glucose meter 2 during rest, exercise, and meal. # represents MARD during exercise is significantly different compared to rest and meal recovery ($P < 0.05$).

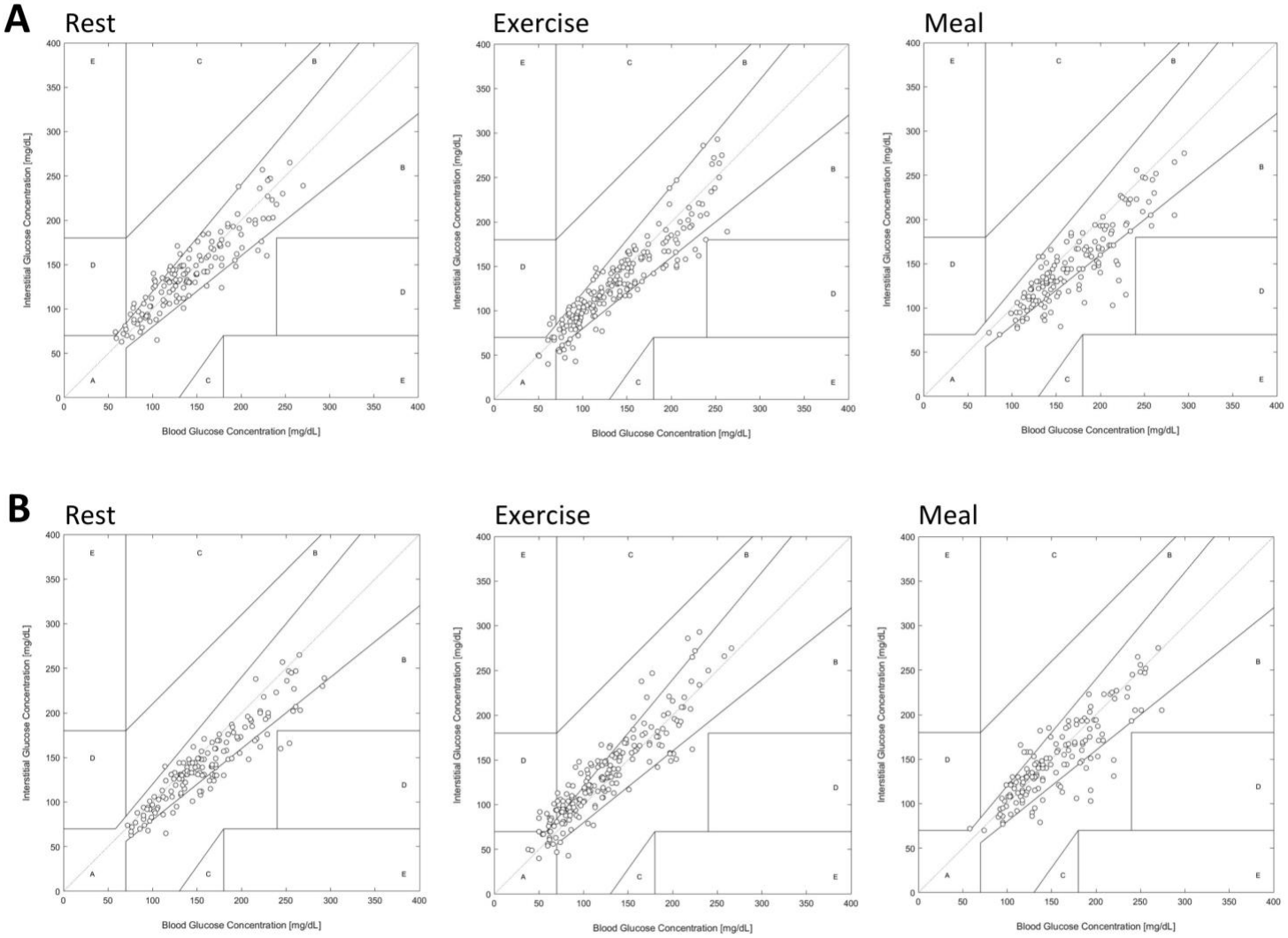


Figure 6.3: Clarke error grids during rest, exercise and meal recovery.

A, Clarke error grids comparing glucose meter 1 with CGM values during rest, exercise, and meal. B, Clarke error grids comparing glucose meter 2 with CGM values during rest, exercise, and meal.

7.0 GENERAL DISCUSSION AND SUMMARY OF FINDINGS

7.1 Discussion

The general goals for clinicians and healthcare practitioners around glycemic management for their patients living with type 1 diabetes is to help improve the percent time spent in a targeted glucose range, reduce the frequency and number of hypoglycemia incidences, and ultimately reduce or maintain HbA_{1c} levels < 7.0%. Individuals with type 1 diabetes are advised to participate in at least 150 minutes of regular physical activity weekly, for a variety of health and fitness reasons, with no more than two days of rest in between and incorporate additional resistance training 2-3 times per week (14). Unfortunately, being physically active with diabetes can sometimes be at odds with the glycemic management goals. Insulin dose adjustments are often required for patients with type 1 diabetes in anticipation of exercise. The amount and type of insulin adjustment will also likely differ depending on the intensive insulin therapy used to manage diabetes (i.e. MDIs vs. CSII). The goal of this thesis is to help develop better glycemic management strategies for a variety of exercise settings in patients with type 1 diabetes using CSII.

For patients using CSII therapy, we showed that insulin pump suspension at the start of a 40-minute bout of continuous steady state moderate intensity exercise leads to a greater drop in blood glucose level compared to vigorous-to-maximal intensity circuit-based exercise (116). In this study, we observed that this type of exercise (i.e. predominantly 'aerobic') not only increased the likelihood of hypoglycemia during activity, but in the 12-hour recovery period post-exercise as well. As such, from this study, it is apparent that pre-exercise insulin reduction is necessary to reduce the likelihood of hypoglycemia.

In general, to reduce the risk of hypoglycemia for prolonged aerobic exercise well after meal absorption (i.e. 3 or more hours after a meal), basal insulin dose reductions are

recommended for patients using CSII ~60–90 minutes before exercise, when possible (13, 14). For vigorous-to-maximal intensity exercise and short duration vigorous-to-maximal intensity resistance exercise, insulin reductions are often not required during exercise, and even a small insulin correction may be required after exercise if hyperglycemia ensues (132).

Patients with type 1 diabetes often experience post-exercise nocturnal hypoglycemia and therefore, a greater emphasis needs to be placed on the importance of rtCGM and more frequent and closer monitoring of blood glucose levels after unusual and prolonged activity. Ideally, planned activity should follow a regular pattern (i.e. same time of day, same intensity, same duration) so that insulin dose strategies can be incorporated routinely with some degree of fine-tuning based on individual responses.

Unfortunately, there is limited clinical research that supports the current exercise guidelines for basal rate reductions in anticipation of aerobic exercise for patients living with type 1 diabetes (13). Even with the current evidence around basal insulin adjustments well in advance of exercise (84, 117), hypoglycemia is still a significant risk for most patients during aerobic exercise. Therefore, we tested the effectiveness of 50% and 80% basal insulin reductions set 90 minutes in advance of aerobic exercise to try and prevent hypoglycemia. We found that a 50-80% basal rate reduction set 90 minutes before aerobic exercise can significantly attenuate the drop in glycemia versus insulin pump suspension at exercise onset (122). Although effective at reducing hypoglycemia during aerobic exercise, future research should also focus on more practical approaches requiring less advanced planning, such as a modified basal rate reduction at exercise start time with some carbohydrate feeding, that can reach a wider patient population.

7.2 Summary of Findings

Academic paper #1 investigated the effects of basal insulin suspension at the start of exercise on blood glucose level during continuous versus circuit-based exercise in individuals with type 1 diabetes on CSII. Although exercise guidelines recommend reducing basal insulin well in advance of exercise, in reality, many individuals with type 1 diabetes disconnect or suspend basal insulin at exercise start, particularly in the case of unplanned exercise. Our findings confirm that during 40 minutes of continuous steady state exercise there was a significantly greater drop in glycemia compared to circuit-based exercise. However, we also found that circuit-based exercise deteriorates blood glucose estimations compared to continuous, moderate-intensity aerobic exercise. This study provides patients and clinicians with valuable insight into how different exercise intensities impact glycemia. Particularly with the increased risk of hypoglycemia during continuous steady state exercise, research studies still need to optimize insulin reduction strategies to prevent hypoglycemia. In summary, if 40 minutes of unplanned CON exercise is being performed, pump suspension at exercise onset likely will not prevent the drop in glycemia and additional carbohydrate feeding may be necessary. Alternatively, with unplanned activity, patients can choose CIRC exercise with pump suspension instead, as the drop in glycemia may not be as drastic.

Academic paper #2 examined the impact of 'pump on' versus 'pump off' on blood glucose concentration during intermittent high intensity exercise and 12 hours in recovery. We found that prolonged intermittent high intensity exercise can be performed with insulin 'pump on' or 'pump off' with no noticeable difference on glycemia during the activity. However, 'pump on' during intermittent high intensity exercise may increase the risk for hypoglycemia in the 12 hours following exercise. Our hypothesis was that 'pump off' would lead to a smaller drop in

glycemia versus 'pump on' during intermittent high intensity exercise. Having found no significant differences in blood glucose levels between conditions, now patients with type 1 diabetes looking to perform up to 40 minutes of intermittent high-intensity exercise have the option of 'pump on' or 'pump off'. These data are especially valuable for patients with type 1 diabetes who prefer to disconnect their insulin pump for comfort reasons during intermittent high intensity exercise because it does not appear to negatively impact glycemia. In fact, in the 12-hour recovery period after exercise, 'pump off' led to less time in hypoglycemia compared to 'pump on' and therefore, may be the preferred strategy during intermittent high intensity exercise.

Academic paper #3 investigated whether a 50% or 80% BRR set 90 minutes before prolonged, continuous steady state exercise can better attenuate the drop in glycemia versus pump suspension at exercise onset in patients with type 1 diabetes on CSII. Based on the findings from academic paper #1 and previously published research (83), we decided to test an earlier BRR strategy in attempt to reduce circulating free insulin levels pre-exercise. In this study, we found that a 50-80% BRR set 90 minutes pre-exercise optimizes glucose control and decreases the risk of hypoglycemia during exercise better than pump suspension at exercise onset. Interestingly, this basal rate reduction set 90 minutes pre-exercise did not compromise the meal recovery glucose control in patients living with type 1 diabetes. Based on the individual blood glucose data, we also found variability in glucose responses among participants during exercise in each of the three BRR strategies. As such, the BRR strategies that we tested were able to effectively attenuate the drop in glycemia during prolonged aerobic exercise. However, it is important to note that one BRR strategy may not apply for all and may still need to be individualized for any given patient.

Academic paper #4 examined the accuracy of rtCGM during prolonged, continuous steady state exercise and during meal recovery in adults living with type 1 diabetes. Our findings confirm that rtCGM underestimates the drop in glycemia during exercise and lags behind blood glucose concentration by ~10-15 mins when glucose levels are changing rapidly. This was the first study to test the accuracy of newer rtCGM technology (Dexcom G4® Platinum with 505 algorithm and G5®) during prolonged continuous steady state exercise. Overall, patients need to be aware of this potential rtCGM time delay as it may impact specific insulin-dosing decisions and/or carbohydrate feeding during exercise. In addition, patients need to be aware of the importance of using the same blood glucose-monitoring device for rtCGM calibrations and regular SMBG testing. Ultimately, whether patients with type 1 diabetes are using rtCGM or SMBG, it is important to increase vigilance and perform more frequent fingerstick capillary glucose monitoring around exercise as additional safety measures. An additional suggestion would be for patients using CSII therapy and rtCGM to set higher limits for low blood glucose alarms during physical activity and exercise. Also, since the accuracy of rtCGM devices is highly correlated with the glucose rate of change, patients with diabetes should attempt to exercise with lower circulating insulin 'on-board' to minimize glucose variability.

7.3 Future Considerations

Although many of the strategies described above should help healthcare providers further promote regular physical activity and exercise for patients with type 1 diabetes, we cannot ignore that recommendations are not always practical and attainable due to the extensive pre-planning required. Therefore, future considerations should include the incorporation of hybrid closed-loop therapy to improve overall glucose control and reduce the likelihood of hypoglycemia in a variety of exercise settings. Studies have already demonstrated that single-hormone (insulin-

only) hybrid closed-loop systems can improve overall glycemic control and reduce HbA_{1c} levels; however, many of these systems still struggle to effectively reduce the initial drop in glycemia that is commonly associated with aerobic exercise and ultimately prevent hypoglycemia (151, 223).

Since a single-hormone hybrid closed-loop system may not be the solution for preventing exercise-associated hypoglycemia, particularly with unplanned exercise, then future research should consider more exercise studies with the use of dual-hormone (insulin and glucagon) hybrid closed-loop systems. Recently, Castle and colleagues (168) showed that the addition of glucagon delivery to a closed-loop system with wearable technology used to detect exercise can reduce hypoglycemia in physically active adults with type 1 diabetes. Despite optimal insulin and glucagon delivery with hybrid closed-loop systems, the main driver of the algorithm is an accurate rtCGM device. In our studies, we showed an important clinical lag in rtCGM technology during aerobic exercise. Further research is required in this area, particularly to consider how different exercise intensities, durations, and times of day can impact glycemia. Industry partners and research need to continue improving the accuracy of all rtCGM devices, particularly when insulin and/or glucagon dosing will be automated in future commercialized hybrid closed-loop devices.

In addition to dual-hormone hybrid closed-loop studies around exercise, a greater focus should be placed on longer duration or exercise training studies in patients with type 1 diabetes. Because the current findings are all based on acute, short-term exercise studies, the data needs to be very carefully interpreted if the outcomes are translated into clinical practice. In addition, as we have shown throughout this thesis, high variability exists among patients with diabetes and therefore, the reproducibility of data may be an additional challenge in this field of research. We

cannot ignore the importance of current acute exercise research studies in patients with type 1 diabetes worldwide; however, more collaborative and multidisciplinary projects will allow for increased sample sizes and potentially more impactful scientific research outcomes. Overall, larger studies will hopefully allow for research outcomes and findings that can be applied to a wider patient population. It is also important to note that our studies were limited to patients with type 1 diabetes using CSII therapy and different strategies are needed for individuals on MDI therapy that have a greater challenge with manipulating basal insulin levels.

To date, there are very few studies published exploring the potential sex-related differences in response to exercise in patients living with type 1 diabetes. Sex-related differences have been extensively studied during exercise and are apparent in individuals *without* diabetes. For example, during aerobic exercise, females generally exhibit higher rates of fat oxidation (236), higher estrogen concentrations (237), and lower catecholamine (specifically epinephrine) responses (238) compared to males. As such, since females tend to deplete less of their glycogen stores during exercise compared to males, they may also experience greater protection of blood glucose concentration during exercise. Whether sex-related differences exist during exercise in patients with type 1 diabetes, but also whether there are possible implications on blood glucose responses during exercise is also presently unknown (207). In the Appendix section of this thesis dissertation, we graph the blood glucose responses during exercise, separated by males and females. Unfortunately, due to the small sample size, we were underpowered and therefore unable to draw inferences on sex-related differences in patients with type 1 diabetes during exercise. Further research is required to investigate any potential sex-related differences during exercise in individuals with type 1 diabetes.

7.4 Conclusions

Overall this thesis dissertation reveals that different basal insulin strategies can be used to improve glucose control depending on the type of activity being performed. We found that pump suspension at exercise onset led to a significantly greater drop in glycemia during CON versus CIRC exercise. During CON exercise, however, participants were better able to estimate their blood glucose concentration when blinded to their measured blood glucose level during activity. We also found that intermittent high intensity exercise can be performed with the insulin 'pump on' or 'pump off' with no noticeable effect on glycemia during the activity. However, 'pump on' during intermittent high intensity exercise may increase hypoglycemia risk in recovery following exercise. In order to reduce the likelihood of hypoglycemia during aerobic exercise and in recovery for individuals living with type 1 diabetes, insulin dose reductions must be made significantly in advance of the activity (90 minutes pre-exercise start) or additional carbohydrate feeding will be required. In addition, we showed that even an acute bout of aerobic exercise can lead to an increased risk of nocturnal hypoglycemia and reducing basal insulin by 20% at bedtime for 6 hours can help combat this risk. Finally, we showed that even with newer rtCGM technology, a clinical lag was observed compared to SMBG during 60 minutes of aerobic exercise. Therefore, increased vigilance and SMBG is recommended before, during, and after exercise for patients with type 1 diabetes. The maintenance of blood glucose concentration in optimal glucose range especially during exercise and in recovery remains one of the biggest obstacles in the lives of many individuals with type 1 diabetes.

8.0 REFERENCES

1. Daneman D. Type 1 diabetes. Lancet. 2006; 367: 847-58.
2. Diabetes Canada Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes. 2018; 42: (Suppl 1):S-S325.
3. Salem MA, Aboelasrar MA, Elbarbary NS, et al. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetol Metab Syndr. 2010; 2: 47-56.
4. Landt KW, Campaigne BN, James FW, et al. Effects of exercise training on insulin sensitivity in adolescents with type I diabetes. Diabetes Care. 1985; 8: 461-5.
5. Zoppini G, Carlini M, Muggeo M. Self-reported exercise and quality of life in young type 1 diabetic subjects. Diabetes Nutr Metab. 2003; 16: 77-80.
6. Kelly D, Hamilton JK, Riddell MC. Blood glucose levels and performance in a sports cAMP for adolescents with type 1 diabetes mellitus: A field study. Int J Pediatr. 2010. doi:10.1155/2010/216167 (online only).
7. Klonoff DC, Ahn D, Drincic A. Continuous glucose monitoring: A review of the technology and clinical use. Diabetes Res Clin Pract. 2017; 133: 178-92.
8. Manohar C, Levine JA, Nandy DK, et al. The effect of walking on postprandial glycemic excursion in patients with type 1 diabetes and healthy people. Diabetes Care. 2012; 35: 2493-9.
9. Orchard TJ, Nathan DM, Zinman B, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA. 2015; 313: 45-53.
10. Warburton DER, Nicol CW, Bredin SSD. Prescribing exercise as preventive therapy. CMAJ. 2006; 174: 961-74.
11. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985; 100: 126-31.

12. Brooks GA, Fahey TD, Baldwin K. Exercise physiology: Human bioenergetics and its applications. 4th Edition ed: New York: McGraw-Hill; 2005.

13. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: A consensus statement. Lancet Diabetes Endocrinol. 2017; 5: 377-90.

14. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. Diabetes Care. 2016; 39: 2065-79.

15. Riddell MC, Zaharieva DP, Yavelberg L, et al. Exercise and the development of the artificial pancreas: One of the more difficult series of hurdles. J Diabetes Sci Technol. 2015; 9: 1217-26.

16. Galassetti P, Riddell MC. Exercise and type 1 diabetes (T1DM). Compr Physiol. 2013; 3: 1309-36.

17. Chamari K, Padulo J. 'Aerobic' and 'Anaerobic' terms used in exercise physiology: A critical terminology reflection. Sports Med Open. 2015; 1: 9. doi 10.1186/s40798-015-0012-1.

18. Bahr R, Grønnerød O, Sejersted OM. Effect of supramaximal exercise on excess postexercise O2 consumption. Med Sci Sports Exerc. 1992; 24: 66-71.

19. Laforgia J, Withers RT, Shipp NJ, et al. Comparison of energy expenditure elevations after submaximal and supramaximal running. J Appl Physiol (1985). 1997; 82: 661-6.

20. Spencer MR, Gastin PB. Energy system contribution during 200- to 1500-m running in highly trained athletes. Med Sci Sports Exerc. 2001; 33: 157-62.

21. Wasserman DH. Four grams of glucose. Am J Physiol Endocrinol Metab. 2009; 296: E11-21.

22. Levine SA, Gordon B, Derick CL. Some changes in the chemical constituents of the blood following a marathon race: with special reference to the development of hypoglycemia. J Am Med Assoc. 1924; 82: 1778-9.

23. Camacho RC, Galassetti P, Davis SN, et al. Glucoregulation during and after exercise in health and insulin-dependent diabetes. Exerc Sport Sci Rev. 2005; 33: 17-23.

24. Mikines KJ, Sonne B, Farrell PA, et al. Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am J Physiol. 1988; 254: E248-59.

25. Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: Implications for diabetes. Diabetes. 2002; 51 (Suppl 1): S271-S83.

26. McArdle WD, Katch FI, Katch VL. Exercise physiology: Nutrition, energy, and human performance. Baltimore, MD: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010.

27. Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Sports Med. 2005; 35: 339-61.

28. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2014; 37: S81-S90.

29. Bozkaya G, Ozgu E, Karaca B. The association between estimated average glucose levels and fasting plasma glucose levels. Clin (Sao Paulo). 2010; 65: 1077-80.

30. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995; 44: 968-83.

31. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: Updated data from the T1D Exchange clinic registry. Diabetes Care. 2015; 38: 971-8.

32. Zinman B, Zuniga-Guajardo S, Kelly D. Comparison of the acute and long-term effects of exercise on glucose control in type I diabetes. Diabetes Care. 1984; 7: 515-9.

33. Roberts L, Jones TW, Fournier PA. Exercise training and glycemic control in adolescents with poorly controlled type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2002; 15: 621-7.

34. Ramalho AC, de Lourdes Lima M, Nunes F. The effect of resistance versus aerobic training on metabolic control in patients with type-1 diabetes mellitus. Diabetes Res Clin Pract. 2006; 72: 271-6.

35. Wong CH, Chiang YC, Wai JP, et al. Effects of a home-based aerobic exercise programme in children with type 1 diabetes mellitus. J Clin Nurs. 2011; 20: 681-91.

36. Galler A, Lindau M, Ernert A, et al. Associations between media consumption habits, physical activity, socioeconomic status, and glycemic control in children, adolescents, and young adults with type 1 diabetes. Diabetes Care. 2011; 34: 2356-9.

37. Mosher P, Nash M, Perry A, et al. Aerobic circuit exercise training: Effect on adolescents with well-controlled insulin-dependent diabetes mellitus. Arch Phys Med Rehabil. 1998; 79: 652-7.

38. Aouadi R, Khalifa R, Aouidet A, et al. Aerobic training programs and glycemic control in diabetic children in relation to exercise frequency. J Sports Med Phys Fitness. 2011; 51: 393-400.

39. Herbst A, Bachran R, Kapellen T, et al. Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. Arch Pediatr Adol Med. 2006; 160: 573-7.

40. Yardley JE, Hay J, Abou-Setta AM, et al. A systematic review and meta-analysis of exercise interventions in adults with type 1 diabetes. Diabetes Res Clin Pract. 2014; 106: 393-400.

41. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care. 2017; 40: 1631-40.

42. Kovatchev B, Cobelli C. Glucose variability: Timing, risk analysis, and relationship to hypoglycemia in diabetes. Diabetes Care. 2016; 39: 502-10.

43. Bergenstal RM, Beck RW, Close KL, et al. Glucose Management Indicator (GMI): A new term for estimating A1c from continuous glucose monitoring. Diabetes Care. 2018; 41: 2275-80.

44. Heise T, Zijlstra E, Nosek L, et al. Pharmacological properties of faster-acting insulin aspart vs insulin aspart in patients with type 1 diabetes receiving continuous subcutaneous insulin infusion: A randomized, double-blind, crossover trial. Diabetes Obes Metab. 2017; 19: 208-15.

45. Subramanian S, Baidal D, Skyler JS, et al. The management of type 1 diabetes. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext. South Dartmouth; 2000.

46. Hirsch IB, Bode BW, Garg S, et al. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care. 2005; 28: 533-8.

47. Lepore G, Corsi A, Dodesini AR, et al. Continuous subcutaneous insulin infusion is better than multiple daily insulin injections in reducing glucose variability only in type 1 diabetes with good metabolic control. Diabetes Care. 2010; 33: e81.

48. Doyle EA, Weinzimer SA, Steffen AT, et al. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. Diabetes Care. 2004; 27: 1554-8.

49. Retnakaran R, Hochman J, DeVries JH, et al. Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1c. Diabetes Care. 2004; 27: 2590-6.

50. Torres I, Ortego J, Valencia I, et al. Benefits of continuous subcutaneous insulin infusion in type 1 diabetes previously treated with multiple daily injections with once-daily glargine and pre-meal analogues. Exp Clin Endocrinol Diabetes. 2009; 117: 378-85.

51. Bruttomesso D, Crazzolara D, Maran A, et al. In Type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine. Diabet Med. 2008; 25: 326-32.

52. Heinemann L, Fleming GA, Petrie JR, et al. Insulin pump risks and benefits: A clinical appraisal of pump safety standards, adverse event reporting and research needs. A joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. Diabetologia. 2015; 58: 862-70.

53. Grunberger G, Bailey TS, Cohen AJ, et al. Statement by the American Association of Clinical Endocrinologists Consensus Panel on insulin pump management. Endocr Pract. 2010; 16: 746-62.

54. Pozzilli P, Battelino T, Danne T, et al. Continuous subcutaneous insulin infusion in diabetes: patient populations, safety, efficacy, and pharmacoeconomics. Diabetes Metab Res Rev. 2016; 32: 21-39.

55. Hellsten Y, Nyberg M. Cardiovascular adaptations to exercise training. Compr Physiol. 2015; 6: 1-32.

56. Dela F, Handberg A, Mikines KJ, et al. GLUT 4 and insulin receptor binding and kinase activity in trained human muscle. J Physiol. 1993; 469: 615-24.

57. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. Physiol Rev. 2013; 93: 993-1017.

58. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. Med Sci Sports Exerc. 2004; 36: 674-88.

59. Kraemer WJ, Adams K, Cafarelli E, et al. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2002; 34: 364-80.

60. Hass CJ, Garzarella L, de Hoyos D, et al. Single versus multiple sets in long-term recreational weightlifters. Med Sci Sports Exerc. 2000; 32: 235-42.

61. Poehlman ET, Dvorak RV, DeNino WF, et al. Effects of resistance training and endurance training on insulin sensitivity in nonobese, young women: a controlled randomized trial. J Clin Endocrinol Metab. 2000; 85: 2463-8.

62. Edmunds S, Roche D, Stratton G, et al. Physical activity and psychological well-being in children with Type 1 diabetes. Psychol Health Med. 2007; 12: 353-63.

63. Moy CS, Songer TJ, LaPorte RE, et al. Insulin-dependent diabetes mellitus, physical activity, and death. Am J Epidemiol. 1993; 137: 74-81.

64. Komatsu W, Gabbay M, Castro M. Aerobic exercise capacity in normal adolescents and those with type 1 diabetes mellitus. Pediatr Diabetes. 2005; 6: 145-9.

65. Yki-Jarvinen H, DeFronzo RA, Koivisto VA. Normalization of insulin sensitivity in type I diabetic subjects by physical training during insulin pump therapy. Diabetes Care. 1984; 7: 520-7.

66. Laaksonen DE, Atalay M, Niskanen LK, et al. Aerobic exercise and the lipid profile in type 1 diabetic men: A randomized controlled trial. Med Sci Sports Exerc. 2000; 32: 1541-8.

67. Rigla M, Sanchez-Quesada JL, Ordonez-Llanos J, et al. Effect of physical exercise on lipoprotein(a) and low-density lipoprotein modifications in type 1 and type 2 diabetic patients. Metabolism. 2000; 49: 640-7.

68. Fuchsjager-Mayrl G, Pleiner J, Wiesinger GF, et al. Exercise training improves vascular endothelial function in patients with type 1 diabetes. Diabetes Care. 2002; 25: 1795-801.

69. Seeger JP, Thijssen DH, Noordam K, et al. Exercise training improves physical fitness and vascular function in children with type 1 diabetes. Diabetes Obes Metab. 2011; 13: 382-4.

70. LaPorte RE, Dorman JS, Tajima N, et al. Pittsburgh insulin-dependent diabetes mellitus morbidity and mortality study: Physical activity and diabetic complications. Pediatrics. 1986; 78: 1027-33.

71. Kriska AM, LaPorte RE, Patrick SL, et al. The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: The Epidemiology of Diabetes Complications Study–VII. J Clin Epidemiol. 1991; 44: 1207-14.

72. Chimen M, Kennedy A, Nirantharakumar K, et al. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. Diabetologia. 2012; 55: 542-51.

73. Jelleyman C, Yates T, O'Donovan G, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: A meta-analysis. Obes Rev. 2015; 16: 942-61.

74. Tonoli C, Heyman E, Roelands B, et al. Effects of different types of acute and chronic (training) exercise on glycaemic control in type 1 diabetes mellitus: A meta-analysis. Sports Med. 2012; 42: 1059-80.

75. Robertson K, Riddell MC, Guinhouya BC, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Exercise in children and adolescents with diabetes. Pediatr Diabetes. 2014; 15 Suppl 20: 203-23.

76. Wood JR, Miller KM, Maahs DM, et al. Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. Diabetes Care. 2013; 36: 2035-7.

77. Brazeau AS, Rabasa-Lhoret R, Strychar I, et al. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care. 2008; 31: 2108-9.

78. Adolfsson P, Riddell MC, Taplin CE, et al. ISPAD clinical practice consensus guidelines 2018: Exercise in children and adolescents with diabetes. Pediatr Diabetes. 2018; 19 Suppl 27: 205-26.

79. Riddell MC, Milliken J. Preventing exercise-induced hypoglycemia in type 1 diabetes using real-time continuous glucose monitoring and a new carbohydrate intake algorithm: An observational field study. Diabetes Technol Ther. 2011; 13: 819-25.

80. Galassetti P, Tate D, Neill R, et al. Effect of antecedent hypoglycemia on counterregulatory responses to subsequent euglycemic exercise in type 1 diabetes. Diabetes. 2003; 52: 1761-9.

81. Tansey MJ, Tsalikian E, Beck RW, et al. The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. Diabetes Care. 2006; 29: 20-5.

82. Mallad A, Hinshaw L, Schiavon M, et al. Exercise effects on postprandial glucose metabolism in type 1 diabetes: A triple tracer approach. Am J Physiol Endocrinol Metab. 2015; 308: E1106-15. doi: 10.1152/ajpendo.00014.2015.

83. Franc S, Daoudi A, Pochat A, et al. Insulin-based strategies to prevent hypoglycaemia during and after exercise in adult patients with type 1 diabetes on pump therapy: The DIABRASPORT randomized study. Diabetes Obes Metab. 2015; 17: 1150-7.

84. McAuley SA, Horsburgh JC, Ward GM, et al. Insulin pump basal adjustment for exercise in type 1 diabetes: A randomised crossover study. Diabetologia. 2016; 59: 1636-44.

85. Gerich JE, Langlois M, Noacco C, et al. Lack of glucagon response to hypoglycemia in diabetes: evidence for an intrinsic pancreatic alpha cell defect. Science (New York, NY). 1973; 182: 171-3.

86. Venables MC, Achten J, Jeukendrup AE. Determinants of fat oxidation during exercise in healthy men and women: a cross-sectional study. J Appl Physiol (1985). 2005; 98: 160-7.

87. Harmer AR, Chisholm DJ, McKenna MJ, et al. High-intensity training improves plasma glucose and acid-base regulation during intermittent maximal exercise in type 1 diabetes. Diabetes Care. 2007; 30: 1269-71.

88. Bally L, Zueger T, Buehler T, et al. Metabolic and hormonal response to intermittent high-intensity and continuous moderate intensity exercise in individuals with type 1 diabetes: a randomised crossover study. Diabetologia. 2016; 59: 776-84.

89. Cryer PE. Hypoglycemia: Still the limiting factor in the glycemic management of diabetes. Endocr Pract. 2008; 14: 750-6.

90. Americna Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: A report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005; 28: 1245-9.

91. Cryer PE. Hypoglycemia in type 1 diabetes mellitus. Endocrinol Metab Clin North Am. 2010; 39: 641-54.

92. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008; 57: 3169-76.

93. Giorda CB, Ozzello A, Gentile S, et al. Incidence and risk factors for severe and symptomatic hypoglycemia in type 1 diabetes. Results of the HYPOS-1 study. Acta Diabetol. 2015; 52: 845-53.

94. McCrimmon R. The mechanisms that underlie glucose sensing during hypoglycaemia in diabetes. Diabet Med. 2008; 25: 513-22.

95. McCrimmon RJ, Sherwin RS. Hypoglycemia in type 1 diabetes. Diabetes. 2010; 59: 2333-9.

96. Fukuda M, Tanaka A, Tahara Y, et al. Correlation between minimal secretory capacity of pancreatic beta-cells and stability of diabetic control. Diabetes. 1988; 37: 81-8.

97. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med. 2004; 350: 2272-9.

98. Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest. 1993; 91: 819-28.

99. Kalra S, Mukherjee JJ, Venkataraman S, et al. Hypoglycemia: The neglected complication. Indian J Endocrinol Metab. 2013; 17: 819-34.

100. Geddes J, Schopman JE, Zammitt NN, et al. Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes. Diabet Med. 2008; 25: 501-4.

101. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes. 1991; 40: 223-6.

102. Cryer PE. Exercise-related hypoglycemia-associated autonomic failure in diabetes. Diabetes. 2009; 58: 1951-2.

103. Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: Reduced awakening from sleep during hypoglycemia. Diabetes. 2003; 52: 1195-203.

104. Cranston I, Lomas J, Maran A, et al. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet. 1994; 344: 283-7.

105. Fanelli C, Pampanelli S, Epifano L, et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia. 1994; 37: 1265-76.

106. Leelarathna L, Little SA, Walkinshaw E, et al. Restoration of self-awareness of hypoglycemia in adults with long-standing type 1 diabetes: Hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. Diabetes Care. 2013; 36: 4063-70.

107. Bhatia V, Wolfsdorf JI. Severe hypoglycemia in youth with insulin-dependent diabetes mellitus: frequency and causative factors. Pediatrics. 1991; 88: 1187-93.

108. Tsalikian E, Mauras N, Beck RW, et al. Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus. J Pediatr. 2005; 147: 528-34.

109. Metcalf KM, Singhvi A, Tsalikian E, et al. Effects of moderate-to-vigorous intensity physical activity on overnight and next-day hypoglycemia in active adolescents with type 1 diabetes. Diabetes Care. 2014; 37: 1272-8.

110. MacDonald MJ. Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes Care. 1987; 10: 584-8.

111. Yardley JE, Kenny GP, Perkins BA, et al. Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes. Diabetes Care. 2012; 35: 669-75.

112. Dube MC, Valois P, Prud'homme D, et al. Physical activity barriers in diabetes: development and validation of a new scale. Diabetes Res Clin Pract. 2006; 72: 20-7.

113. Brazeau AS, Mircescu H, Desjardins K, et al. The Barriers to Physical Activity in Type 1 Diabetes (BAPAD-1) scale: Predictive validity and reliability. Diabetes Metab. 2012; 38: 164-70.

114. Zaharieva DP, Riddell MC. Insulin management strategies for exercise in diabetes. Can J Diabetes. 2017; 41: 507-16.

115. Admon G, Weinstein Y, Falk B, et al. Exercise with and without an insulin pump among children and adolescents with type 1 diabetes mellitus. Pediatrics. 2005; 116: 348-55.

116. Zaharieva D, Yavelberg L, Jamnik V, et al. The effects of basal insulin suspension at the start of exercise on blood glucose levels during continuous versus circuit-based exercise in individuals with type 1 diabetes on continuous subcutaneous insulin infusion. Diabetes Technol Ther. 2017; 19: 370-8.

117. Roy-Fleming A, Taleb N, Messier V, et al. Timing of insulin basal rate reduction to reduce hypoglycemia during late post-prandial exercise in adults with type 1 diabetes using insulin pump therapy: A randomized crossover trial. Diabetes Metab. 2018. doi: 10.1016/j.diabet.2018.08.002.

118. Shetty G, Wolpert H. Insulin pump use in adults with type 1 diabetes--practical issues. Diabetes Technol Ther. 2010; 12 Suppl 1: S11-6.

119. Heinemann L, Nosek L, Kapitza C, et al. Changes in basal insulin infusion rates with subcutaneous insulin infusion: time until a change in metabolic effect is induced in patients with type 1 diabetes. Diabetes Care. 2009; 32: 1437-9.

120. Yardley JE, Kenny GP, Perkins BA, et al. Resistance versus aerobic exercise: Acute effects on glycemia in type 1 diabetes. Diabetes Care. 2013; 36: 537-42.

121. Taplin CE, Cobry E, Messer L, et al. Preventing post-exercise nocturnal hypoglycemia in children with type 1 diabetes. J Pediatr. 2010; 157: 784-8.

122. Zaharieva D, McGaugh S, Pooni R, et al. Optimized open-loop glucose control and time in range with basal insulin reduction 90 minutes before aerobic exercise in patients with type 1 diabetes on continuous subcutaneous insulin infusion. Diabetes Care (In submission). 2018.

123. Rabasa-Lhoret R, Bourque J, Ducros F, et al. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). Diabetes Care. 2001; 24: 625-30.

124. Guelfi KJ, Jones TW, Fournier PA. The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. Diabetes Care. 2005; 28: 1289-94.

125. Bussau VA, Ferreira LD, Jones TW, et al. The 10-s maximal sprint: a novel approach to counter an exercise-mediated fall in glycemia in individuals with type 1 diabetes. Diabetes Care. 2006; 29: 601-6.

126. Campbell MD, Walker M, Trenell MI, et al. Large pre- and postexercise rapid-acting insulin reductions preserve glycemia and prevent early- but not late-onset hypoglycemia in patients with type 1 diabetes. Diabetes Care. 2013; 36: 2217-24.

127. Shetty VB, Fournier PA, Davey RJ, et al. Effect of exercise intensity on glucose requirements to maintain euglycemia during exercise in type 1 diabetes. J Clin Endocrinol Metab. 2016; 101: 972-80.

128. Campbell MD, Walker M, Trenell MI, et al. Metabolic implications when employing heavy pre- and post-exercise rapid-acting insulin reductions to prevent hypoglycaemia in type 1 diabetes patients: a randomised clinical trial. PloS One. 2014; 9: e97143. doi: 10.1371/journal.pone.0097143.

129. Campbell MD, Walker M, Bracken RM, et al. Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: a randomized controlled trial. BMJ Open Diabetes Res Care. 2015; 3: e000085. doi: 10.1136/bmjdrc-2015-000085

130. West DJ, Morton RD, Bain SC, et al. Blood glucose responses to reductions in pre-exercise rapid-acting insulin for 24 h after running in individuals with type 1 diabetes. J Sports Sci. 2010; 28: 781-8.

131. Moser O, Tschakert G, Mueller A, et al. Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin. PloS One. 2015; 10: e0136489. doi: 10.1371/journal.pone.0136489.

132. Turner D, Luzio S, Gray BJ, et al. Algorithm that delivers an individualized rapid-acting insulin dose after morning resistance exercise counters post-exercise hyperglycaemia in people with type 1 diabetes. Diabetic Med. 2016; 33: 506-10.

133. Gallen I. Exercise in type 1 diabetes. Diabet Med. 2003; 20 Suppl 1: 2-5.

134. Grimm JJ, Ybarra J, Berné C, et al. A new table for prevention of hypoglycaemia during physical activity in type 1 diabetic patients. Diabetes Metab. 2004; 30: 465-70.

135. Adolfsson P, Mattsson S, Jendle J. Evaluation of glucose control when a new strategy of increased carbohydrate supply is implemented during prolonged physical exercise in type 1 diabetes. Eur J Appl Physiol. 2015; 115: 2599-607.

136. Jeukendrup A. A step towards personalized sports nutrition: carbohydrate intake during exercise. Sports Med. 2014; 44 Suppl 1: S25-33.

137. Cox DJ, Clarke WL, Gonder-Frederick L, et al. Accuracy of perceiving blood glucose in IDDM. Diabetes Care. 1985; 8: 529-36.

138. Kropff J, Bruttomesso D, Doll W, et al. Accuracy of two continuous glucose monitoring systems: a head-to-head comparison under clinical research centre and daily life conditions. Diabetes Obes Metab. 2015; 17: 343-9.

139. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ. 2011; 343: d3805. doi: 10.1136/bmj.d3805.

140. Kato N, Cui J, Kato M. Structured self-monitoring of blood glucose reduces glycated hemoglobin in insulin-treated diabetes. J Diabetes Investig. 2013; 4: 450-3.

141. Joo EY, Lee JE, Kang HS, et al. Frequency of self-monitoring of blood glucose during the school day Is associated with the optimal glycemic control among Korean adolescents with type 1 diabetes. Diabetes Metab J. 2018. doi: 10.4093/dmj.2018.0018.

142. DeSalvo D, Buckingham B. Continuous glucose monitoring: current use and future directions. Curr Diab Rep. 2013; 13: 657-62.

143. McMahon SK, Ferreira LD, Ratnam N, et al. Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. J Clin Endocrinol Metab. 2007; 92: 963-8.

144. Gomez AM, Gomez C, Aschner P, et al. Effects of performing morning versus afternoon exercise on glycemic control and hypoglycemia frequency in type 1 diabetes patients on sensor-augmented insulin pump therapy. J Diabetes Sci Technol. 2015; 9: 619-24.

145. Iscoe KE, Corcoran M, Riddell MC. High rates of nocturnal hypoglycemia in a unique sports camp for athletes with type 1 diabetes: Lessons learned from continuous glucose monitoring systems. Can J Diabetes. 2008; 32: 182-9.

146. Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018; 41: S1-S2.

147. Riddlesworth TD, Beck RW, Gal RL, et al. Optimal sampling duration for continuous glucose monitoring to determine long-term glycemic control. Diabetes Technol Ther. 2018; 20: 314-6.

148. Rodbard D. Continuous glucose monitoring: A review of successes, challenges, and opportunities. Diabetes Technol Ther. 2016; 18 Suppl 2: S3-S13.

149. Adolfsson P, Parkin CG, Thomas A, et al. Selecting the appropriate continuous clucose monitoring system - a practical approach. Eur Endocrinol. 2018; 14: 24-9.

150. Boughton CK, Hovorka R. Is an artificial pancreas (closed-loop system) for type 1 diabetes effective? Diabet Med. 2018. doi: 10.1111/dme.13816.

151. Turksoy K, Hajizadeh I, Hobbs N, et al. Multivariable artificial pancreas for various exercise types and intensities. Diabetes Technol Ther. 2018; 20: 662-71.

152. Clarke WL, Anderson S, Breton M, et al. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience. J Diabetes Sci Technol. 2009; 3: 1031-8.

153. Hovorka R, Kumareswaran K, Harris J, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. BMJ. 2011; 342.

154. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: A phase 2 randomised crossover trial. Lancet. 2010; 375: 743-51.

155. Kovatchev B, Cheng P, Anderson SM, et al. Feasibility of long-term closed-loop control: A multicenter 6-month trial of 24/7 automated insulin delivery. Diabetes Technol Ther. 2017; 19: 18-24.

156. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther. 2017; 19: 155-63.

157. Sherr JL, Cengiz E, Palerm CC, et al. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. Diabetes Care. 2013; 36: 2909-14.

158. Breton MD, Cherñavvsky DR, Forlenza GP, et al. Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: The artificial pancreas ski study. Diabetes Care. 2017; 40: 1644-50.

159. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med. 2013; 368: 824-33.

160. Ly TT, Weinzimer SA, Maahs DM, et al. Automated hybrid closed-loop control with a proportional-integral-derivative based system in adolescents and adults with type 1 diabetes: individualizing settings for optimal performance. Pediatr Diabetes. 2017; 18: 348-55.

161. Jacobs PG, El Youssef J, Reddy R, et al. Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. Diabetes Obes Metab. 2016; 18: 1110-9.

162. Adams RN, Tanenbaum ML, Hanes SJ, et al. Psychosocial and human factors during a trial of a hybrid closed loop system for type 1 diabetes management. Diabetes Technol Ther. 2018; 20: 648-53.

163. Sinha M, McKeon KM, Parker S, et al. A comparison of time delay in three continuous glucose monitors for adolescents and adults. J Diabetes Sci Technol. 2017; 11: 1132-7.

164. Garg SK, Voelmle M, Gottlieb PA. Time lag characterization of two continuous glucose monitoring systems. Diabetes Res Clin Pract. 2010; 87: 348-53.

165. Basu A, Dube S, Veettil S, et al. Time lag of glucose from intravascular to interstitial compartment in type 1 diabetes. J Diabetes Sci Technol. 2015; 9: 63.

166. Kulcu E, Tamada JA, Reach G, et al. Physiological differences between interstitial glucose and blood glucose measured in human subjects. Diabetes Care. 2003; 26: 2405-9.

167. Schmelzeisen-Redeker G, Schoemaker M, Kirchsteiger H, et al. Time delay of CGM sensors: Relevance, causes, and countermeasures. J Diabetes Sci Technol. 2015; 9: 1006-15.

168. Castle JR, El Youssef J, Wilson LM, et al. Randomized outpatient trial of single- and dual-hormone closed-loop systems that adapt to exercise using wearable sensors. Diabetes Care. 2018; 41: 1471-77.

169. Haidar A, Smaoui MR, Legault L, et al. The role of glucagon in the artificial pancreas. Lancet Diabetes Endocrinol. 2016; 4: 476-9.

170. Caputo N, Castle JR, Bergstrom CP, et al. Mechanisms of glucagon degradation at alkaline pH. Peptides. 2013; 45: 40-7.

171. Wilson LM, Castle JR. Stable liquid glucagon: Beyond emergency hypoglycemia rescue. J Diabetes Sci Technol. 2018; 12: 847-53.

172. Guelfi KJ, Ratnam N, Smythe GA, et al. Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. Am J Physiol Endocrinol Metab. 2007; 292: 865-70.

173. Bussau VA, Ferreira LD, Jones TW, et al. A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. Diabetologia. 2007; 50: 1815-8.

174. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: Effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. Diabetic Med. 2011; 28: 824-32.

175. Cassidy S, Thoma C, Houghton D, et al. High-intensity interval training: A review of its impact on glucose control and cardiometabolic health. Diabetologia. 2016; 60: 7-23.

176. Tsalikian E, Kollman C, Tamborlane WB, et al. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. Diabetes Care. 2006; 29: 2200-4.

177. Freund A, Johnson SB, Rosenbloom A, et al. Subjective symptoms, blood glucose estimation, and blood glucose concentrations in adolescents with diabetes. Diabetes Care. 1986; 9: 236-43.

178. Jamnik VK, Warburton DE, Makarski J, et al. Enhancing the effectiveness of clearance for physical activity participation: Background and overall process. Appl Physiol Nutr Metab. 2011; 36: S3-S13.

179. Howley ET, Bassett DR, Welch HG. Criteria for maximal oxygen uptake: Review and commentary. Med Sci Sports Exerc. 1995; 27: 1292-301.

180. Clarke WL, Cox D, Gonder-Frederick LA, et al. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. Diabetes Care. 1987; 10: 622-8.

181. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986; 1: 307-10.

182. Pinsker JE, Kraus A, Gianferante D, et al. Techniques for exercise preparation and management in adults with type 1 diabetes. Can J Diabetes. 2016; 40: 503-8.

183. Turksoy K, Paulino TML, Zaharieva DP, et al. Classification of Physical Activity: Information to Artificial Pancreas Control Systems in Real Time. J Diabetes Sci Technol. 2015; 9: 1200-7.

184. Frayn KN, Karpe F. Regulation of human subcutaneous adipose tissue blood flow. Int J Obes (Lond). 2014; 38: 1019-26.

185. Al Khalifah RA, Suppère C, Haidar A, et al. Association of aerobic fitness level with exercise-induced hypoglycaemia in Type 1 diabetes. Diabet Med. 2016.

186. American Diabetes Association. Physical activity/exercise and diabetes. Diabetes Care. 2004; 27 Suppl 1: S58-62.

187. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. Diabetes Care. 2004; 27: 1761-73.

188. Riddell MC, Bar-Or O. Childen and adolescents. In: Handbook of exercise and diabetes. ed: Ruderman N, Devlin JT, Schneider SH, Kriska A. Alexandria, Virginia: American Diabetes Association; 2002. p. 547-66.

189. Moser O, Mader JK, Tschakert G, et al. Accuracy of continuous glucose monitoring (CGM) during continuous and high-intensity interval exercise in patients with type 1 diabetes mellitus. Nutrients. 2016; 8: E489. doi: 10.3390/nu8080489.

190. Bally L, Zueger T, Pasi N, et al. Accuracy of continuous glucose monitoring during differing exercise conditions. Diabetes Res Clin Pract. 2016; 112: 1-5.

191. Taleb N, Emami A, Suppere C, et al. Comparison of two continuous glucose monitoring systems, Dexcom G4 Platinum and Medtronic Paradigm Veo Enlite system, at rest and during exercise. Diabetes Technol Ther. 2016; 18: 561-7.

192. Charlton J, Kilbride L, MacLean R, et al. Delayed hypoglycaemia in people with type 1 diabetes after performing moderate intensity exercise before the evening meal. Pract Diab. 2015; 32: 99-102.

193. Maran A, Pavan P, Bonsembiante B, et al. Continuous glucose monitoring reveals delayed nocturnal hypoglycemia after intermittent high-intensity exercise in nontrained patients with type 1 diabetes. Diabetes Technol Ther. 2010; 12: 763-8.

194. Guelfi K. Intermittent high-intensity exercise does not increase the risk of early postexercise hypoglycemia in Individuals with type 1 diabetes. Diabetes Care. 2005; 28:416-8.

195. Adams OP. The impact of brief high-intensity exercise on blood glucose levels. Diabetes Metab Syndr Obes. 2013; 6: 113-22.

196. Rempel M, Yardley JE, MacIntosh A, et al. Vigorous intervals and hypoglycemia in type 1 diabetes: A randomized cross over trial. Sci Rep. 2018; 8: 15879. doi: 10.1038/s41598-018-34342-6.

197. Perkins B. Type 1 diabetes and exercise: Using the insulin pump to maximum advantage. Can J Diabetes. 2006; 30: 72-9.

198. Ruegemer JJ, Squires RW, Marsh HM, et al. Differences between prebreakfast and late afternoon glycemic responses to exercise in IDDM patients. Diabetes Care. 1990; 13: 104-10.

199. Trefts E, Williams AS, Wasserman DH. Exercise and the regulation of hepatic metabolism. Prog Mol Biol Transl Sci. 2015; 135: 203-25.

200. Dubé M-C, Weisnagel SJ, Prud'homme D, et al. Exercise and newer insulins: How much glucose supplement to avoid hypoglycemia? Med Sci Sports Exerc. 2005; 37: 1276-82.

201. Riddell MC, Bar-Or O, Ayub BV, et al. Glucose ingestion matched with total carbohydrate utilization attenuates hypoglycemia during exercise in adolescents with IDDM. Int J Sport Nutr. 1999; 9: 24-34.

202. Bracken RM, West DJ, Stephens JW, et al. Impact of pre-exercise rapid-acting insulin reductions on ketogenesis following running in type 1 diabetes. Diabetic Med. 2011; 28: 218-22.

203. Sigal RJ, Armstrong MJ, Bacon SL, et al. Physical Activity and Diabetes. Can J Diabetes. 2018; 42 Suppl 1: S54-S63.

204. Diabetes Research in Children Network Study G, Tsalikian E, Kollman C, et al. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. Diabetes Care. 2006; 29: 2200-4.

205. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994; 17: 697-703.

206. Clarke WL, Cox DJ, Gonder-Frederick LA, et al. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995; 18: 517-22.

207. Brockman NK, Yardley JE. Sex-related differences in fuel utilization and hormonal response to exercise: Implications for individuals with type 1 diabetes. Appl Physiol Nutr Metab. 2018: 1-12.

208. Péronnet F, Massicotte D. Table of nonprotein respiratory quotient: An update. Can J Sport Sci. 1991; 16: 23-9.

209. Klonoff DC, Parkes JL, Kovatchev BP, et al. Investigation of the accuracy of 18 marketed blood glucose monitors. Diabetes Care. 2018; 41: 1681-8.

210. Riddell MC, Zaharieva DP, Tansey M, et al. Individual glucose responses to prolonged moderate intensity aerobic exercise in adolescents with type 1 diabetes: The higher they start, the harder they fall. Pediatr Diabetes. 2018 [Epub ahead of print]. doi: 10.1111/pedi.12799.

211. Wilson DM, Calhoun PM, Maahs DM, et al. Factors associated with nocturnal hypoglycemia in at-risk adolescents and young adults with type 1 diabetes. Diabetes Technol Ther. 2015; 17: 385-91.

212. Nakagawa S, Nakayama H, Sasaki T, et al. A simple method for the determination of serum free insulin levels in insulin-treated patients. Diabetes. 1973; 22: 590-600.

213. Agesen RM, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogs on frequency of non-severe hypoglycemia in patients with type 1 diabetes prone to severe hypoglycemia: Much higher rates detected by continuous glucose monitoring than by delf-monitoring of blood glucose-The HypoAna Trial. Diabetes Technol Ther. 2018; 20: 247-56.

214. United States Food and Drug Administration Advisory Panel. FDA Advisory Panel Votes to Recommend Non-Adjunctive Use of Dexcom G5 Mobile CGM. Diabetes Technol Ther. 2016; 18: 512-6.

215. Pettus J, Edelman SV. Recommendations for using real-time continuous glucose monitoring (rtCGM) data for insulin adjustments in type 1 diabetes. J Diabetes Sci Technol. 2017; 11: 138-47.

216. Laffel LM, Aleppo G, Buckingham BA, et al. A practical approach to using trend arrows on the Dexcom G5 CGM system to manage children and adolescents with diabetes. J Endocr Soc. 2017; 1: 1461-76.

217. Kovatchev BP, Patek SD, Ortiz EA, et al. Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. Diabetes Technol Ther. 2015; 17: 177-86.

218. Davey RJ, Low C, Jones TW, et al. Contribution of an intrinsic lag of continuous glucose monitoring systems to differences in measured and actual glucose concentrations changing at variable rates in vitro. J Diabetes Sci Technol. 2010; 4: 1393-9.

219. Keenan B, Mastrototaro JJ, Voskanyan G, et al. Delays in minimally invasive continuous glucose monitoring devices: A review of current technology. J Diabetes Sci Technol. 2009; 3: 1207-14.

220. Biagi L, Bertachi A, Quirós C, et al. Accuracy of continuous glucose monitoring before, during, and after aerobic and anaerobic exercise in patients with type 1 diabetes mellitus. Biosensors. 2018; 8: E22. doi: 10.3390/bios8010022.

221. Adolfsson P, Nilsson S, Lindblad B. Continuous glucose monitoring system during physical exercise in adolescents with type 1 diabetes. Acta Paediatr (Oslo, Norway : 1992). 2011; 100: 1603-9.

222. Hortensius J, Slingerland RJ, Kleefstra N, et al. Self-monitoring of blood glucose: The use of the first or the second drop of blood. Diabetes Care. 2011; 34: 556-60.

223. Zaharieva DP, Riddell MC, Henske J. The accuracy of continuous glucose monitoring and flash glucose monitoring during aerobic exercise in type 1 diabetes. J Diabetes Sci Technol. 2018. doi: 10.1177/1932296818804550.

224. Ekhlaspour L, Mondesir D, Lautsch N, et al. Comparative accuracy of 17 point-of-care glucose meters. J Diabetes Sci Technol. 2017; 11: 558-66.

225. Yardley JE, Sigal RJ, Kenny GP, et al. Point accuracy of interstitial continuous glucose monitoring during exercise in type 1 diabetes. Diabetes Technol Ther. 2013; 15: 46-9.

226. Bailey TS. Clinical Implications of Accuracy Measurements of continuous glucose sensors. Diabetes Technol Ther. 2017; 19: S51-S4.

227. Leelarathna L, Nodale M, Allen JM, et al. Evaluating the accuracy and large inaccuracy of two continuous glucose monitoring systems. Diabetes Technol Ther. 2013; 15: 143-9.

228. Andelin M, Kropff J, Matuleviciene V, et al. Assessing the accuracy of continuous glucose monitoring (CGM) calibrated with capillary values using capillary or venous glucose levels as a reference. J Diabetes Sci Technol. 2016; 10: 876-84.

229. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes Care. 2010; 33: 17-22.

230. Battelino T, Conget I, Olsen B, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomised controlled trial. Diabetologia. 2012; 55: 3155-62.

231. Wong JC, Foster NC, Maahs DM, et al. Real-time continuous glucose monitoring among participants in the T1D Exchange clinic registry. Diabetes Care. 2014; 37: 2702-9.

232. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD randomized clinical trial. JAMA. 2017; 317: 379-87.

233. Turksoy K, Quinn LT, Littlejohn E, et al. An integrated multivariable artificial pancreas control system. J Diabetes Sci Technol. 2014; 8: 498-507.

234. Jafri RZ, Balliro CA, El-Khatib F, et al. A three-way accuracy comparison of the Dexcom G5, Abbott Freestyle Libre Pro, and Senseonics Eversense CGM devices in an outpatient study of subjects with type 1 diabetes. Diabetes. 2018; 67: 14. doi: 10.2337/db18-14-OR.

235. Giani E, Macedoni M, Barilli A, et al. Performance of the Flash Glucose Monitoring system during exercise in youth with type 1 diabetes. Diabetes Res Clin Pract. 2018. doi: 10.1016/j.diabres.2018.10.001.

236. Horton TJ, Pagliassotti MJ, Hobbs K, et al. Fuel metabolism in men and women during and after long-duration exercise. J Appl Physiol (1985). 1998; 85: 1823-32.

237. Jurkowski JE, Jones NL, Walker C, et al. Ovarian hormonal responses to exercise. J Appl Physiol Respir Environ Exerc Physiol. 1978; 44: 109-14.

238. Davis SN, Galassetti P, Wasserman DH, et al. Effects of gender on neuroendocrine and metabolic counterregulatory responses to exercise in normal man. J Clin Endocrinol Metab. 2000; 85: 224-30.

239. Forlenza GP, Argento NB, Laffel LM. Practical Considerations on the use of continuous glucose monitoring in pediatrics and older adults and nonadjunctive use. Diabetes Technol Ther. 2017; 19: S13-S20.

240. Ólafsdóttir AF, Polonsky W, Bolinder J, et al. A randomized clinical trial of the effect of continuous glucose monitoring on nocturnal hypoglycemia, daytime hypoglycemia, glycemic variability, and hypoglycemia confidence in persons with type 1 diabetes Treated with Multiple Daily Insulin Injections (GOLD-3). Diabetes Technol Ther. 2018; 20: 274-84.

241. Patton SR, Clements MA. Continuous glucose monitoring versus self-monitoring of blood glucose in children with type 1 diabetes: Are there pros and cons for both? US Endocrinol. 2012; 8: 27-9.

242. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med. 2010; 363: 311-20.

243. Wood A, O'Neal D, Furler J, et al. Continuous glucose monitoring: a review of the evidence, opportunities for future use and ongoing challenges. Intern Med J. 2018; 48: 499-508.

244. Wilson DM, Beck RW, Tamborlane WV, et al. The accuracy of the FreeStyle Navigator continuous glucose monitoring system in children with type 1 diabetes. Diabetes Care. 2007; 30: 59-64.

245. Siegmund T, Heinemann L, Kolassa R, et al. Discrepancies between blood glucose and interstitial glucose-technological artifacts or physiology: Implications for selection of the appropriate therapeutic target. J Diabetes Sci Technol. 2017; 11: 766-72.

246. Moser O, Yardley JE, Bracken RM. Interstitial glucose and physical exercise in type 1 diabetes: Integrative physiology, technology, and the gap in-between. Nutrients. 2018; 10: E93. doi: 10.3390/nu10010093.

247. Kumareswaran K, Elleri D, Allen JM, et al. Accuracy of continuous glucose monitoring during exercise in type 1 diabetes pregnancy. Diabetes Technol Ther. 2013; 15: 223-9.

248. Turner D, Luzio S, Gray BJ, et al. Impact of single and multiple sets of resistance exercise in type 1 diabetes. Scand J Med Sci Sports. 2015; 25: 99-109.

249. Davey RJ, Paramalingam N, Retterath AJ, et al. Antecedent hypoglycaemia does not diminish the glycaemia-increasing effect and glucoregulatory responses of a 10 s sprint in people with type 1 diabetes. Diabetologia. 2014; 57: 1111-8.

250. Larson NS, Pinsker JE. The role of continuous glucose monitoring in the care of children with type 1 diabetes. Int J Pediatr Endocrinol. 2013; 2013: 8.

251. Rickels MR, DuBose SN, Toschi E, et al. Mini-dose glucagon as a novel approach to prevent exercise-induced hypoglycemia in type 1 diabetes. Diabetes Care. 2018; 41: 1909-16.

9.0 APPENDICES

Appendix A: CGM Accuracy – Supplemental Paper

The accuracy of continuous glucose monitoring and flash glucose monitoring during aerobic exercise in type 1 diabetes

Dessi P. Zaharieva, M.Sc.[1], Michael C. Riddell, Ph.D.[1, 2], and Joseph Henske, M.D.[3]

Author Affiliations:
[1]York University, Department of Kinesiology & Health Science, Muscle Health Research Centre, Toronto, ON, Canada; [2]LMC Diabetes & Endocrinology, Toronto, ON, Canada; [3]DuPage Medical Group, Glen Ellyn, IL, USA

Abbreviations: (CGM) Continuous glucose monitoring, (SMBG) self-monitoring of blood glucose, (rtCGM) real-time CGM, (FGM) flash glucose monitor, (T1D) type 1 diabetes, (MARD) mean absolute relative difference, (CSII) continuous subcutaneous insulin infusion, (YSI) Yellow Springs Instruments, (HCL) hybrid closed-loop, (SD) standard deviation

Keywords: Accuracy, continuous glucose monitoring, exercise, self-monitoring of blood glucose, sensors, type 1 diabetes

Corresponding Author: Dr. Joseph Henske, MD, FACE; DuPage Medical Group, Chicago, IL, USA

Conflict-of-Interest Disclosure: DPZ has received speaker's honoraria from Medtronic Diabetes and Ascensia Diabetes. MCR has received speaker's honoraria from Medtronic Diabetes, Insulet, Ascensia Diabetes, Novo Nordisk (via JDRF PEAK Program), Xeris Pharmaceuticals, Lilly Diabetes, and Lilly Innovation. JH has received speaker's honoraria from Dexcom and Novo Nordisk (via JDRF PEAK Program). No other potential conflicts of interest relevant to this article were reported.

Figure and Table Count: 1 figure, 3 tables

Funding Source: None

Acknowledgements: None

Abstract

Background: Continuous glucose monitoring (CGM) devices capture glucose excursions better than self-monitoring of blood glucose (SMBG). However, the accuracy of CGM devices, specifically around exercise and insulin-dosing decisions remains a concern.

Methods: In this case study, one physically active male with T1D, using a hybrid closed-loop system, completed 13 continuous steady state moderate intensity or aerobic exercise sessions to compare the accuracy of two real-time CGM (rtCGM) devices, one flash glucose monitor (FGM) and SMBG.

Results: At the onset of exercise, glucose levels were significantly higher with FGM (237 ± 45 mg/dL) versus rtCGM1 (198 ± 34 mg/dL, P=0.0001), rtCGM2 (206 ± 35 mg/dL, P=0.0001), and SMBG (215 ± 33 mg/dL, P=0.003), respectively. FGM values rose transiently (P=0.0001) after the start of exercise and remained higher than all other devices until 30 minutes of aerobic exercise (P<0.05).

Conclusion: During periods of relatively stable glucose concentrations, rtCGM and FGM may correlate well with SMBG; however, a lag effect is observed during steady state moderate-intensity exercise in individuals with T1D. Both rtCGM and FGM devices tend to overestimate glucose values with moderate-intensity exercise therefore, the threshold for carbohydrate feeding during aerobic exercise should be initiated at a much higher glucose when using rtCGM or FGM devices compared to SMBG.

Introduction

Continuous glucose monitoring (CGM) devices are emerging as the standard of care for managing type 1 diabetes (T1D) (146, 161, 239). These new tools allow for the convenience of frequent monitoring in a variety of settings and they detect more hypo- and hyperglycemic events compared to frequent self-monitoring of blood glucose (SMBG) (41, 240-242). In the context of exercise, they are also valuable in detecting activity-related dysglycemia in youth with T1D (221). Improvements in accuracy have led to non-adjunctive status, so that insulin dosing and hypoglycemic management decisions are possible with several devices (214-216). For current and emerging commercial products that modulate continuous subcutaneous insulin infusion (CSII), and for future devices that may deliver glucagon as well, efficacy and safety of these devices are largely predicated on the accuracy of the integrated CGM.

Despite non-adjunctive insulin dosing indications in some of these devices, the use of CGM readings for decision-making without confirmatory fingerstick glucose measurements remains a concern. Specifically, precautions should be taken during circumstances of rapid changes in glucose (e.g. following a meal, during exercise), when symptoms do not match blood glucose readings, and in patients with end-stage renal dysfunction, pregnancy, liver disease, and other edematous states (7, 226, 243). The physiologic lag in equilibrium between interstitial and blood glucose, which may be anywhere between 5-15 minutes (165, 167, 218, 219, 244), can cause a clinically important discrepancy between CGM and SMBG during moderate-to-intense physical activity (174, 189, 225, 245-247). Due to this lag effect, it remains unclear whether CGM use during aerobic activity is adequate for glucose management decisions, including when to initiate carbohydrate replacement to avoid hypoglycemia and determine the appropriate amount and/or timing of carbohydrate ingestion.

Blood glucose levels tend to fall with continuous steady state moderate intensity or aerobic exercise (81, 84, 116) and rise with vigorous-to-maximal intensity exercise (87, 248, 249). Previous studies have shown reduced CGM accuracy during exercise due to the lag effect combined with rapidly changing glucose levels resulting in a large absolute difference between sensor glucose and the laboratory standard (e.g. Yellow Springs Instrument [YSI] glucose analyzer) (190, 191, 220).

The data presented here examined the concurrent use of three commonly used glucose-monitoring devices (two real-time continuous glucose monitors (rtCGM), and one flash glucose monitor [FGM]) in conjunction with SMBG during aerobic exercise to determine whether the information derived from these devices could be used effectively to guide carbohydrate intake to avoid hypoglycemia.

Methods

A male subject with T1D (age 40 years; diabetes duration 25 years; HbA_{1c} 6.5%; and body mass index 24.9), experienced in marathon running was studied over two months. He averaged ~25 miles of moderate-intensity running per week in 3-4 workouts. Written informed consent was obtained from the participant for this case report. The subject reported no significant diabetes-related complications or hypoglycemia unawareness based a score of two for the Clarke and Gold questionnaires, respectively (205, 206).

The subject wore a Food and Drug Administration (FDA) approved HCL insulin delivery system (Medtronic MiniMed 670G insulin pump with HCL algorithm, Guardian® Sensor 3 glucose sensor with Guardian Link 3 transmitter [Minneapolis, MN, USA], rtCGM1), Dexcom G5® mobile CGM system (San Diego, CA, USA), rtCGM2, and Abbott FreeStyle Libre FGM system (Chicago, IL, USA). The FGM was placed on the upper arm while the rtCGM devices

were placed on the abdomen or upper buttocks at least 24 hours prior to exercise. SMBG and all calibrations were performed using a Contour® Next Link glucose meter (Ascensia Diabetes Care, Parsippany, NJ, USA) according to manufacturer recommendations.

To reduce the likelihood of hypoglycemia, and based on personal experience, the HCL insulin pump was placed in an 'exercise target mode' (i.e. target set to 150 mg/dL) one-hour prior to the onset of exercise, disconnected during exercise, and reconnected immediately following exercise. Pre-exercise meals were consumed > four hours prior to exercise with usual insulin dosing, to help minimize the drop in glucose during exercise due to residual bolus insulin (13). To achieve a starting blood glucose target of 180-200 mg/dL, carbohydrate supplementation (16-20g) was used 60 minutes prior to exercise if blood glucose levels were below this range.

In each session, SMBG were recorded 10-minutes before and after exercise and every 10-minutes during exercise. A total of 13 exercise sessions were completed over a period of two months, each consisting of ~60 minutes of running per session, either outdoors on a flat course or on a treadmill with a consistent pace of 7 minutes and 15 seconds per mile, at a moderate-intensity. Carbohydrate gels (GU Energy Gel, 22g of maltodextrin, Berkeley, CA) were used to avoid hypoglycemia based on SMBG values and rate of change based on previous experiences (absolute SMBG < 140 mg/dL with decrease > 2 mg/dL/min (one straight down trend arrow on the Dexcom G5® mobile CGM system) or < 180 mg/dL with rapidly changing blood glucose > 3 mg/dL/min (two straight down trend arrows on the Dexcom G5®).

Statistical Analysis

Glucose measurements among all devices (SMBG, rtCGM1, rtCGM2, and FGM) were compared using a two-way repeated measures ANOVA. MARD was calculated using the

difference between the reference glucose meter (SMBG) and glucose-monitoring device (rtCGM1, rtCGM2, and FGM) and dividing it by the reference, then multiplied by 100. A one-way ANOVA was used to compare the difference between MARD across all devices when complete datasets were available (12 sessions had complete data across all glucose monitoring devices). In addition, a one-way ANOVA was used to compare devices at the start and end of exercise, the glucose at which point carbohydrate was initiated, and the rate of change in glucose at the time of carbohydrate ingestion. Tukey's post hoc multiple comparisons test was used when significant interactions were found. All analyses were conducted using GraphPad Prism version 7.0 (GraphPad Software, CA, USA). All of the data are represented as mean ± standard deviation (SD) and the statistical significance was set *a priori* to $P < 0.05$, unless otherwise indicated.

Results

Full datasets capturing glucose data from SMBG and all three interstitial glucose-monitoring devices were captured in 12 of 13 exercise sessions. Missing data occurred for one rtCGM2 device because of signal loss.

Table A1 represents the results of glucose testing across all devices and carbohydrate intake during aerobic exercise, while Table A2 shows the statistical comparisons across all of the devices. Capillary blood glucose concentrations, as measured by SMBG, dropped rapidly during exercise, from 215 ± 33 to 104 ± 23 mg/dL ($P = 0.0001$) even with significant carbohydrate intake (60 ± 24 grams per session) and the HCL system set to an 'exercise target mode' one hour before exercise and the pump suspended during activity. SMBG values were markedly lower (by about 30-35%) than the three glucose-monitoring devices, particularly the FGM that tended to show a transient rise in glucose concentrations. Moreover, the rate of change (i.e. drop rate) in

glucose at the initiation of carbohydrate feeding was much higher with SMBG (4.0 ± 1.8 mg/dL/min) versus rtCGM1 (0.8 ± 1.6 mg/dL/min) ($P = 0.002$).

Table A3 represents the MARD during rest and exercise when comparing SMBG to each glucose-monitoring device (rtCGM1, rtCGM2, and FGM, respectively). MARD was lower at rest compared to exercise when comparing SMBG to all other devices (Table A3). Specifically, during rest, rtCGM2 was significantly lower compared to FGM ($P = 0.02$). During exercise, the MARD for rtCGM1 and rtCGM2 was significantly lower than the MARD for FGM (both $P < 0.001$).

Figure A1 illustrates glucose data from the three glucose-monitoring devices and SMBG across the 13 exercise sessions. Based on repeated measures ANOVA, a trial by time interaction was found ($P = 0.0001$). At exercise onset, glucose levels were higher with FGM (237 ± 45 mg/dL) versus rtCGM1 (198 ± 34 mg/dL, $P = 0.0001$), rtCGM2 (206 ± 35 mg/dL, $P = 0.0001$), and SMBG (215 ± 33 mg/dL, $P = 0.003$), respectively. FGM values rose transiently ($P = 0.0001$) after the start of exercise and remained higher than all other devices until 30 minutes of exercise ($P < 0.05$). SMBG values were lower than FGM from the start until the cessation of exercise ($P < 0.05$). SMBG were also lower than rtCGM1 and rtCGM2 from 10- to 50-minutes of exercise (both $P < 0.05$). Figure A2 is the supplemental information that represents individual glucose data for all devices (rtCGM1, rtCGM2, FGM, and SMBG) across the 13 exercise sessions.

Discussion

This case study demonstrates that while rtCGM and FGM may correlate well with SMBG during periods of relative glucose stability, a clinically important lag effect is observed during aerobic exercise when glucose levels are declining rapidly. This discrepancy between SMBG and

interstitial glucose monitoring devices (i.e. rtCGM and FGM) may impact critical decision-making for carbohydrate replacement during planned exercise and routine physical activity.

This study also demonstrates that the absolute differences in glucose concentration between SMBG and rtCGM or FGM were greatest in the first 30 minutes after the onset of exercise as blood glucose levels showed the most rapid decline. Interestingly, FGM reported significantly higher readings compared to all other devices during the first 30 minutes of activity and frequently reported a rise after the start of exercise (Figure A1).

Individuals with T1D tend to require carbohydrate feeding during prolonged aerobic exercise and often use CGM trend arrows to guide when to initiate feeding (182, 250). The amount of carbohydrate intake required to avoid hypoglycemia varies depending on the intensity and duration of exercise, familiarity of activity, and other factors (13). In this case study, during aerobic exercise, carbohydrate intake of ~ 60 ± 24 grams per hour (i.e. 0.73 g/kg/hr) was sufficient to prevent hypoglycemia when ingested as glucose levels began dropping. It is notable that SMBG levels dropped markedly during exercise despite using a HCL system set in 'exercise target mode' 60 minutes pre-exercise and with pump suspension during exercise- further highlighting the challenge that aerobic exercise places on developing HCL systems (15).

Given that the accuracy of glucose monitoring devices appears dependent on the glucose rate of change, efforts should be made to minimize glucose variability by considering insulin 'on-board' and intensity and type of exercise. The use of mini-dose glucagon in a HCL system during exercise or subcutaneously prior to exercise may emerge as an effective alternative to insulin reduction and increased carbohydrate intake (161, 251).

Limitations of this case study include the use of SMBG as a reference compared to all glucose monitoring devices since YSI glucose was not available (226-228). However, use of

capillary versus venous blood for CGM accuracy is generally associated with significantly lower MARD values (228).

Conclusions

Due to the observed lag in interstitial glucose as compared to SMBG during exercise, we recommend to initiate carbohydrate feeding sooner (i.e. when glucose is ~200 mg/dL and dropping) when the patient is relying on rtCGM or FGM devices for decision-making. Whether this recommendation holds true for all exercise situations remains unclear. Future studies should increase the sample size and include women, children, and adolescents. In addition, the potential impact of rtCGM and FGM device location and day-of-wear on accuracy should also be investigated.

Author Contributions Statement

JH contributed to the conception and design of the study; JH was responsible for the data collection for this case study. DPZ and MCR were responsible for statistical analysis. DPZ, MCR, and JH each wrote sections of the manuscript. All authors contributed to manuscript revisions. All authors read and approved the submitted version.

Funding Sources

No funding sources were involved in this study.

Tables & Figures

Table A1: Glucose testing and carbohydrate intake during 60 minutes of steady state, continuous exercise.

	SMBG (Contour Next)	**rtCGM1** (Guardian®)	**rtCGM2** (Dexcom G5®)	**FGM** (FreeStyle Libre)
Glucose at exercise onset (mg/dL)	215 ± 33	198 ± 34	206 ± 35	237 ± 45
Glucose after 60-min exercise (mg/dL)	104 ± 23	120 ± 26	120 ± 32	141 ± 29
Glucose at which carbohydrate intake initiated	143 ± 32	194 ± 43	196 ± 34	225 ± 45
Rate of glucose drop (mg/dL/min) **at time carbohydrate intake initiated**	4.0 ± 1.8	0.8 ± 1.6	1.9 ± 1.8	1.9 ± 2.7

Note: Data represents mean ± SD.

Table A2: Statistical analysis of "glucose testing and carbohydrate intake during 60 minutes of steady state, continuous exercise" (as shown above).

	SMBG vs. rtCGM1	**SMBG vs. rtCGM2**	**SMBG vs. FGM**	**rtCGM1 vs. rtCGM2**	**rtCGM1 vs. FGM**	**rtCGM2 vs. FGM**
Glucose at exercise onset (mg/dL)	X				X	X
Glucose after 60-min exercise (mg/dL)			X		X	X
Glucose at which carbohydrate intake initiated	X	X	X		X	X
Rate of glucose drop (mg/dL/min) **at time carbohydrate intake initiated**	X	X				

Note: 'X' represents statistically significant difference between devices ($P < 0.05$).

Table A3: Mean absolute relative difference (MARD) comparing SMBG to rtCGM1, rtCGM2, and FGM during rest and during exercise

	rtCGM1 (Guardian®)	**rtCGM2** (Dexcom G5®)	**FGM** (FreeStyle Libre)
MARD at Rest (%)	9 ± 5	6 ± 6 *	11 ± 8
MARD During Exercise (%)	29 ± 24	31 ± 21	44 ± 24 #

Note: Data represents mean±SD, * significantly different from FGM; P=0.02. # significantly different from rtCGM1 and rtCGM2 (both $P < 0.001$).

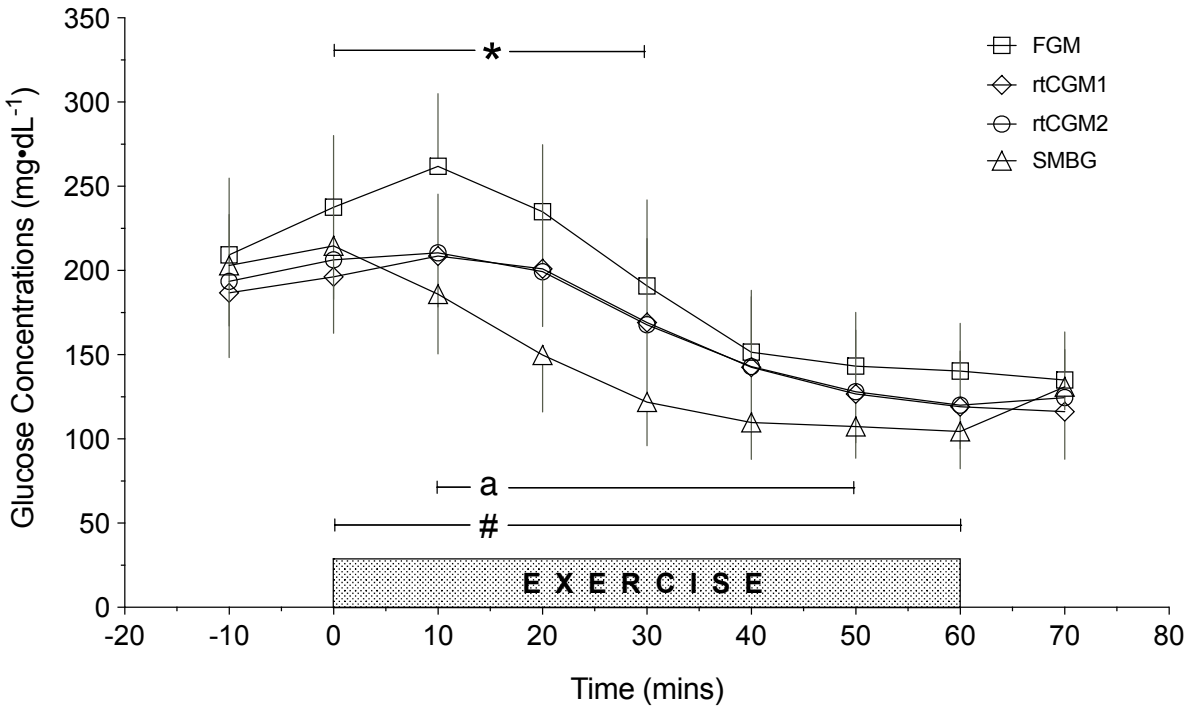


Figure A1: Absolute glucose concentrations for all devices (rtCGM1, rtCGM2, FGM, and SMBG) across 13 exercise sessions. * indicates that FGM is significantly higher than all other device (rtCGM1, rtCGM2, and SMBG), α indicates that SMBG values are significantly lower than both rtCGM1 and rtCGM2, and # indicates that SMBG remained significantly lower than FGM values from the start to the end of exercise. Significance was set to $P<0.05$.

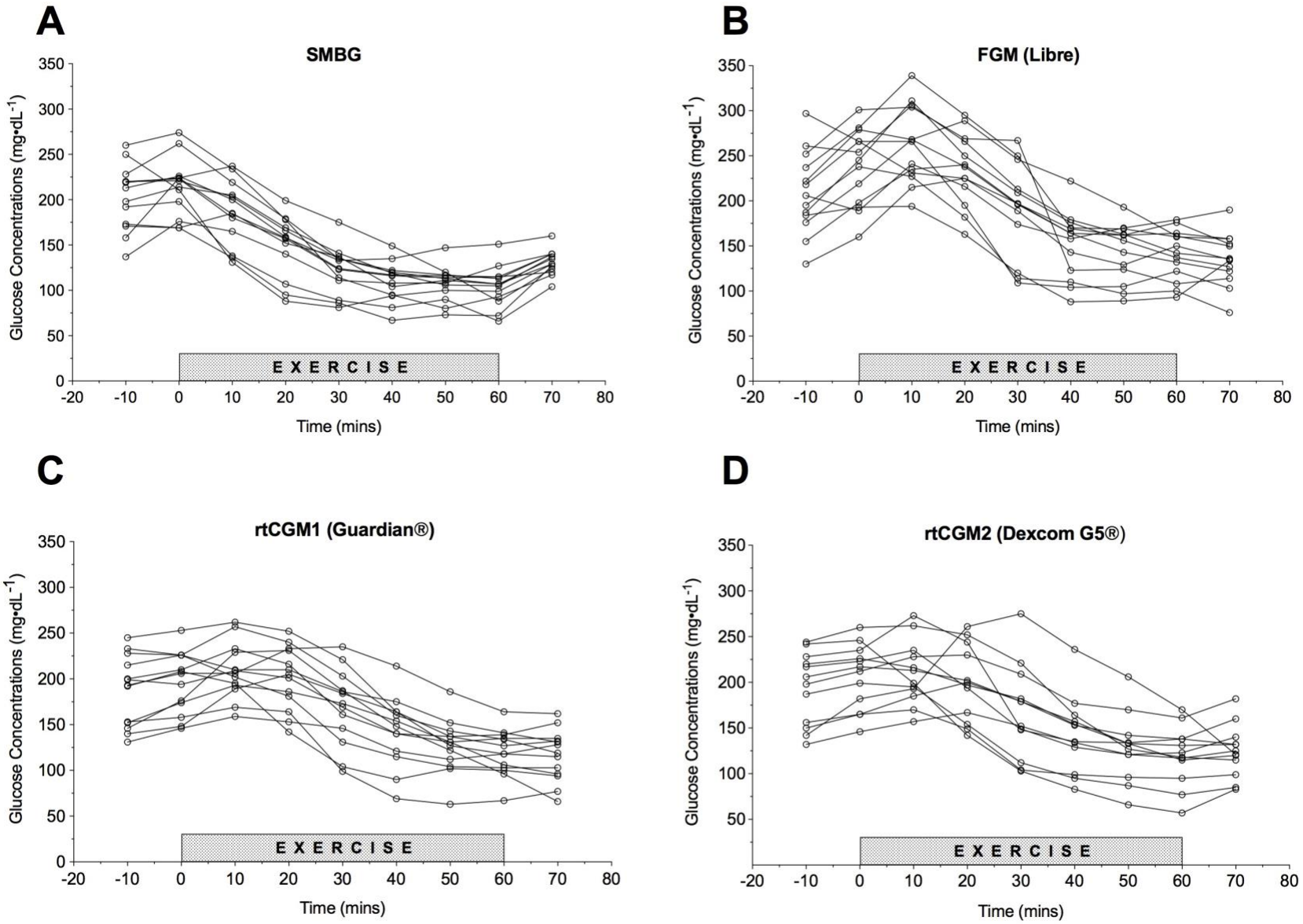


Figure A2: Additional individual glucose data for all devices (rtCGM1, rtCGM2, FGM, and SMBG) across 13 exercise sessions.

Appendix B: Ethics Approval

Study #1 & #2: Adjusting insulin pump basal levels for exercise in adults with T1D

YORK UNIVERSITÉ UNIVERSITY **OFFICE OF RESEARCH ETHICS (ORE)**

Memo

To: Dr. Michael Riddell, Kinesiology and Health Science

From: , Sr. Manager and Policy Advisor, Research Ethics

Issue Date: Tue Jan 20 2015

Expiry Date: Wed Jan 20 2016

RE: **Adjusting insulin pump basal levels for exercise in adults with type 1 diabetes**
Certificate #: e2015 - 009

I am writing to inform you that the Human Participants Review Sub-Committee has reviewed and approved the above project.

Should you have any questions, please feel free to contact me at:

Yours sincerely,

Sr. Manager and Policy Advisor,
Office of Research Ethics

Study #3 & #4: Omnipod type 1 diabetes insulin management for exercise study (OmniTIME Study)

OFFICE OF RESEARCH ETHICS (ORE)

Memo

To:	Michael Riddell, Kinesiology
From:	Sr. Manager and Policy Advisor, Research Ethics
Issue Date:	Wed Mar 01 2017
Expiry Date:	Thu Mar 01 2018
RE:	**OmniPod Type 1 diabetes Insulin Management for Exercise study (Omni-TIME-study)** **Certificate #: e2017 - 073**

I am writing to inform you that the Human Participants Review Sub-Committee has reviewed and approved the above project.

Should you have any questions, please feel free to contact me at:

Yours sincerely,

Sr. Manager and Policy Advisor,
Office of Research Ethics

Appendix C: Questionnaires

Physical Activity Readiness Questionnaire for Everyone:

2018 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	**YES**	**NO**
1) Has your doctor ever said that you have a heart condition ☐ OR high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:** _____	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it ***does not limit your current ability*** to be physically active. **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

☑ **If you answered NO to all of the questions above, you are cleared for physical activity.**
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

PARTICIPANT DECLARATION
If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness centre may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

01-11-2017

2018 PAR-Q+

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthritis, Osteoporosis, or Back Problems?

If the above condition(s) is/are present, answer questions 1a-1c — If **NO** ☐ go to question 2

1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	YES ☐ NO ☐
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	YES ☐ NO ☐

2. Do you currently have Cancer of any kind?

If the above condition(s) is/are present, answer questions 2a-2b — If **NO** ☐ go to question 3

2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and/or neck?	YES ☐ NO ☐
2b.	Are you currently receiving cancer therapy (such as chemotheraphy or radiotherapy)?	YES ☐ NO ☐

3. Do you have a Heart or Cardiovascular Condition? *This includes Coronary Artery Disease, Heart Failure, Diagnosed Abnormality of Heart Rhythm*

If the above condition(s) is/are present, answer questions 3a-3d — If **NO** ☐ go to question 4

3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
3b.	Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction)	YES ☐ NO ☐
3c.	Do you have chronic heart failure?	YES ☐ NO ☐
3d.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	YES ☐ NO ☐

4. Do you have High Blood Pressure?

If the above condition(s) is/are present, answer questions 4a-4b — If **NO** ☐ go to question 5

4a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
4b.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure)	YES ☐ NO ☐

5. Do you have any Metabolic Conditions? *This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes*

If the above condition(s) is/are present, answer questions 5a-5e — If **NO** ☐ go to question 6

5a.	Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physician-prescribed therapies?	YES ☐ NO ☐
5b.	Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness.	YES ☐ NO ☐
5c.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, **OR** the sensation in your toes and feet?	YES ☐ NO ☐
5d.	Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney disease, or liver problems)?	YES ☐ NO ☐
5e.	Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future?	YES ☐ NO ☐

2018 PAR-Q+

6. Do you have any Mental Health Problems or Learning Difficulties? *This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome*

If the above condition(s) is/are present, answer questions 6a-6b — If **NO** ☐ go to question 7

6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
6b.	Do you have Down Syndrome **AND** back problems affecting nerves or muscles?	YES ☐ NO ☐

7. Do you have a Respiratory Disease? *This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure*

If the above condition(s) is/are present, answer questions 7a-7d — If **NO** ☐ go to question 8

7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
7b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	YES ☐ NO ☐
7c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	YES ☐ NO ☐
7d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	YES ☐ NO ☐

8. Do you have a Spinal Cord Injury? *This includes Tetraplegia and Paraplegia*

If the above condition(s) is/are present, answer questions 8a-8c — If **NO** ☐ go to question 9

8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
8b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	YES ☐ NO ☐
8c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	YES ☐ NO ☐

9. Have you had a Stroke? *This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event*

If the above condition(s) is/are present, answer questions 9a-9c — If **NO** ☐ go to question 10

9a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
9b.	Do you have any impairment in walking or mobility?	YES ☐ NO ☐
9c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	YES ☐ NO ☐

10. Do you have any other medical condition not listed above or do you have two or more medical conditions?

If you have other medical conditions, answer questions 10a-10c — If **NO** ☐ read the Page 4 recommendations

10a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months?	YES ☐ NO ☐
10b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	YES ☐ NO ☐
10c.	Do you currently live with two or more medical conditions?	YES ☐ NO ☐

PLEASE LIST YOUR MEDICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE: _____

_____

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.

2018 PAR-Q+

If you answered NO to all of the FOLLOW-UP questions (pgs. 2-3) about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

If you answered **YES** to **one or more of the follow-up questions** about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ **at www.eparmedx.com** before becoming more physically active.
- Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- All persons who have completed the PAR-Q+ please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact
www.eparmedx.com
Email: eparmedx@gmail.com

Citation for PAR-Q+
Warburton DER, Jamnik VK, Bredin SSD, and Gledhill N (on behalf of the PAR-Q+ Collaboration). The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and Electronic Physical Activity Readiness Medical Examination (ePARmed-X+). Health & Fitness Journal of Canada 4(2):3-23, 2011.

Key References

1. Jamnik VK, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, and Gledhill N. Enhancing the effectiveness of clearance for physical activity participation: background and overall process. APNM 36(S1):S3-S13, 2011.
2. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, Charlesworth S, and Shephard RJ. Evidence-based risk assessment and recommendations for physical activity clearance: Consensus Document. APNM 36(S1):S266-s298, 2011.
3. Chisholm DM, Collis ML, Kulak LL, Davenport W, and Gruber N. Physical activity readiness. British Columbia Medical Journal. 1975;17:375-378.
4. Thomas S, Reading J, and Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Canadian Journal of Sport Science. 1992;17:4:338-345.

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the BC Ministry of Health Services.

01-11-2017

Hypoglycemia Awareness Questionnaires:

Clarke Score: Survey items used to categorize aware or having reduced awareness of hypoglycemia in subjects

1) Check the category that best describes you (check one only):

_____ I always have symptoms when my blood sugar is low
_____ I sometimes have symptoms when my blood sugar is low
_____ I no longer have symptoms when my blood sugar is low

2) Have you lost some of the symptoms that used to occur when your blood sugar was low?

_____ Yes _____ No

3) In the past 6 months, how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself)

_____ Never _____ Once or twice
_____ Every other month _____ Once a month
_____ More than once a month

4) In the past year, how often have you had severe hypoglycemia episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose)

_____ Never _____ 1 time _____ 2 times _____ 3 times
_____ 4 times _____ 5 times _____ 6 times _____ 7 times
_____ 8 times _____ 9 times _____ 10 times _____ 11 times
_____ 12 or more times

5) How often in the last month have you had readings < 3.9 mmol/L with symptoms?

_____ Never _____ 1 to 3 times _____ 1 time/week
_____ 2 to 3 times/week _____ 4 to 5 times/week _____ Almost daily

6) How often in the last month have you had readings < 3.9 mmol/L without any symptoms?

_____ Never _____ 1 to 3 times _____ 1 time/week
_____ 2 to 3 times/week _____ 4 to 5 times/week _____ Almost daily

7) How low does your blood sugar need to go before you feel symptoms?

_____ 3.4-3.9 mmol/L _____ 2.8-3.3 mmol/L
_____ 2.2-2.7 mmol/L _____ < 2.2 mmol/L

8) To what extent can you tell by your symptoms that your blood sugar is low?

_____ Never _____ Rarely
_____ Sometimes _____ Often
_____ Always

The Gold Score:

Do you know when your hypos are commencing? Please circle a number:

	Always Aware						Never Aware
Awareness:	1	2	3	4	5	6	7

Medical Health Questionnaire:

Medical History

Name: (First, Last)		
Age:		
DOB: (mm/dd/yyyy)		
Sex:	Male	Female
Email Address:		
Phone Number:		

When were you diagnosed with diabetes? (Date, including year)		
What type of insulin pump are you currently using? • Medtronic, Animas, One Touch, OmniPod, etc.		
How long have you been on insulin pump therapy? (Approximately)		
What type of insulin are you using? • Novorapid, Humalog, Lantus, etc.		
What was your last Hb_{A1c} reading? When was it?		
Have you ever worn a Continuous Glucose Monitor (CGM)? (If YES) How long have you been using one?	YES	NO
Have you had any severe hypoglycemic episodes in the last 6 months? Severe = Hospitalizations If so, when?	YES	NO

What are your current basal rates if on insulin pump? (List below)					

How active are you? (Circle below)				
Not Active (0-1 day(s) a week)	**Mild** (2-3 days a week)	**Moderate** (4-5 days a week)	**Active** (6+ days a week)	**Elite** (National or international level sport)

What is your TOTAL, daily insulin dose (average)? _____ units
Sedentary day: _____

ANTHROPOMETRICS
1. Sex: □ M □ F
2. Date of birth (dd/mm/yyyy): __ __ / __ __ / __ __ __ __ Age: _____
3. a) Dominant hand: □ L □ R
4. Race/Ethnicity: □ White □ American Indian/Alaska Native/Native Canadian □ Asian □ Native Hawaiian or Other Pacific Islander □ Black or African American □ Other: _____
5. Weight: ___ ___ ___ . ___ kg /lbs (circle kg or lbs)
6. Height: ___ ___ ___ . ___ cm/in (circle cm or in)
7. Systolic BP (SBP): (1) ___ ___ ___ mm Hg (2) ___ ___ ___ mm Hg **Average:** ___ ___ ___ mm Hg
8. Diastolic BP (DBP): (1) ___ ___ ___ mm Hg (2) ___ ___ ___ mm Hg **Average:** ___ ___ ___ mm Hg
9. Resting/Basal Heart Rate (HR): (1) ___ ___ ___ bpm (2) ___ ___ ___ bpm **Average:** ___ ___ ___ bpm
10. Allergies: a) Latex: □ Y □ N Other(s): _____ b) Food restrictions (e.g. vegetarian/celiac/lactose): _____
11. Menstruation (approximate date of menstruation): _____ (or N/A)
12. a) Percent body fat (Tanita %): _____ b) NIH Waist Circumference (cm): _____

13. **MEDICATIONS**			
1. NAME OF MEDICATION	TYPE	TABS (digits)	DOSAGE (mg)
	□ Statin □ B-blocker □ Anti-platelet □ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca^+ chan. Block □ Birth control □ Ace inhibit □ Other anti-HTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_____		
2. NAME OF MEDICATION	TYPE	TABS (digits)	DOSAGE (mg)
	□ Statin □ B-blocker □ Anti-platelet □ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca^+ chan. Block □ Birth control □ Ace inhibit □ Other anti-HTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_____		
3. NAME OF MEDICATION	TYPE	TABS (digits)	DOSAGE (mg)
	□ Statin □ B-blocker □ Anti-platelet □ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca^+ chan. Block □ Birth control □ Ace inhibit □ Other anti-HTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_____		
4. NAME OF MEDICATION	TYPE	TABS (digits)	DOSAGE (mg)
	□ Statin □ B-blocker □ Anti-platelet □ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca^+ chan. Block □ Birth control □ Ace inhibit □ Other anti-HTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_____		

DIABETES INFORMATION

14. Date of Diagnosis (dd/mm/yyyy): __ __ / __ __ / __ __ __ __

15. Type of Regimen: ☐ OmniPod ☐ Other: _____

16. Current Basal Rates:

(a) _____ (U/hr) + Time (e) _____ (U/hr)

(b) _____ (U/hr) + Time (f) _____ (U/hr)

(c) _____ (U/hr) + Time (g) _____ (U/hr)

(d) _____ (U/hr) + Time (h) _____ (U/hr)

17. Type of Insulin:

□ NPH □ Lantus/Insulin Glargine □ Novorapid/Insulin Aspart □ Novolin 30/70

□ Lente □ Levemir/Insulin Detemir □ Apidra/Glulisine □ Humulin N

□ Ultralente □ Regular Insulin □ Humalog/Insulin Lispro

18. Diabetes Complications:

Has a doctor ever told the patient they have:

High blood pressure □ Y □ N Nephropathy □ Y □ N

Retinopathy □ Y □ N Neuropathy □ Y □ N

19. Does the patient have a history of cardiovascular disease? □ Y □ N

If yes, further details:

_____

20. History of Lows:

When the patient feels low, do they test and record their blood glucose? □ Y □ N

Do they treat with carbohydrates? □ Y □ N

Does the low usually resolve itself within ~15 minutes? □ Y □ N

Do they usually feel (know) when they are low? □ Y □ N

21. Has the patient been hospitalized due to hypoglycemia and/or required 3rd party assistance in the past 6 months? □ Y □ N

22. Current glucometer (make/model): _____

23. Total daily insulin dose (average): _____ Units

PERSONAL CONTACT INFORMATION

1. Your Complete Legal Name

First | **Middle**

Last

2. Address

Street Address

(PO Box/Apt #)

City | **Province** | **Postal Code**

3. Telephone

Home: ___ ___ ___ - ___ ___ ___ - ___ ___ ___ ___

Work: ___ ___ ___ - ___ ___ ___ - ___ ___ ___ ___

Cell: ___ ___ ___ - ___ ___ ___ - ___ ___ ___ ___

4. Email

EMERGENCY CONTACT INFORMATION

1. Name of Emergency Contact & Relationship to Participant

First

Last

Relationship to Participant:

2. Telephone

Home: ___ ___ ___ - ___ ___ ___ - ___ ___ ___ ___

Work: ___ ___ ___ - ___ ___ ___ - ___ ___ ___ ___

Cell: ___ ___ ___ - ___ ___ ___ - ___ ___ ___ ___

3. Email

Appendix D: Recruitment Flyers

Do you have Type 1 Diabetes? Are you on an insulin pump?

Participate in an artificial pancreas exercise study now!

Participants will complete 3 visits to the Human Performance Laboratory at York University.

1) Treadmill test to measure maximal aerobic capacity
2) Aerobic steady-state exercise on treadmill
3) Anaerobic, interval circuit training

Participants will be provided with continuous glucose monitor, sports armband, and bioharness during exercise visits

Please contact Dessi Zaharieva for further information and study details!

YORK UNIVERSITÉ UNIVERSITY

redefine THE POSSIBLE.

OmniTIME Study

New Study

Researchers at York University (Toronto, Keele Campus) are conducting a study on strategies to prevent low blood sugars during exercise in individuals living with Type 1 diabetes using the **Omnipod® Insulin Management System.**

Selected participants will get:

- A fitness assessment
- A chance to wear a continuous glucose monitor (CGM)

This study involves:

- 4 exercise visits at York University
- 3 different basal insulin adjustments:
  - 80% reduction 90-mins pre-exercise
  - 50% reduction 90-mins pre-exercise
  - 100% reduction at start of exercise

YORK UNIVERSITÉ UNIVERSITY

If you are between the ages of 18–65 years and are interested in learning more, please contact Dessi

Note: Insulet Canada Corporation is a supporter of this study.

Appendix E: Consent Forms

Informed Consent Form 1

Date: _____

Project Title: Adjusting insulin pump basal levels for exercise in youth and adults with type 1 diabetes.

Principal Investigators:
Dr. Michael Riddell, Ph.D. (Professor)

Principal Student Investigator:
Dessi Zaharieva (Ph.D. Candidate, 2014)

Dr. Veronica Jamnik, Ph.D. (Associate Professor)

Purpose of the Research: The purpose of the study is to determine the ideal basal rate adjustments using insulin pump therapy during various exercise modalities in individuals with type 1 diabetes. This is phase 1 of a 4-year projected project that will be carried out at York University in the Human Performance Laboratory under the co-supervision of Dr. Michael Riddell and Dr. Veronica Jamnik. Future studies will use these basal rate adjustments together with the artificial pancreas algorithm to monitor blood glucose concentrations during physical activity and daily living. The overall goal is to improve diabetes management and create more freedom in the lives of those affected by type 1 diabetes.

This research will be presented at conferences in the future, although no specific conference has been selected at this time. We also aim to publish this data in an academic journal, and share the information with the companies involved (Medtronic Inc., Canada, Vancive Medical, USA, and Zephyr Technology Corporation, USA). All participants will remain anonymous.

What You Will Be Asked to Do in the Research: A total of 4 sessions will be required for this project. All visits will be carried out at York University in the Fitness Laboratory of Dr. Jamnik, located at 126 Bethune. The first will be a familiarization session that requires completed informed consent, anthropometric measurements, continuous glucose monitor connection, medical history questionnaire, PAR-Q Plus questionnaire, and an initial V_{O2max} test. This session is estimated to take approximately 1.5 hours. The subsequent sessions will be three experimental trials of steady-state aerobic exercise as well as anaerobic circuit exercise. The experimental sessions (3) will require a bioharness strapped around the chest to measure physiological variables including heart rate, energy expenditure, etc. and finger capillary blood glucose (BG) measurements. These sessions will take ~2 hours each to complete.
Familiarization Session (Visit 1): During this session, you will be asked to complete the medical history questionnaire and informed consent. A Physical Activity Readiness Questionnaire (PAR-

Q+) will also be conducted to measure your pre-exercise health. An example of a question on the PAR-Q+ questionnaire includes: "Has your doctor ever said that you have a heart condition or high blood pressure: Yes or No". You will then have your height, weight, and body fat measured. An investigator of the same sex will conduct your measurements of body fat using skinfold calipers and this will be done in a private room. You will also be asked to complete a test of your maximal oxygen consumption (VO_{2max}) by running on a treadmill while the speed and incline are increased every 2 minutes until you reach exhaustion. You will be asked to refrain from drinking caffeinated beverages or ingesting caffeine supplements for the day of each experimental trial.

Experimental Sessions (Visit 2-4): You will be provided with a continuous glucose monitor (CGM) for the duration of the study and asked to insert the CGM on the same day as Visit 2. Upon entry to the laboratory, you will be asked to check your own BG levels using a contour link glucometer (Bayer, Canada) provided. Also, 10-minutes prior to exercise, a BG measurement will be taken. The first exercise protocol will consist of a 40-minute jog on a treadmill at ~40-50% of VO_{2max}. Regular finger capillary blood samples will be collected every 10-15-minutes during exercise. You will be asked to prick your own finger using your own lancing device during the experimental portion. Once the exercise session is complete, you will be asked to remain in the laboratory for 30-minutes for additional BG measurements and to ensure hypoglycemic episodes do not occur post-exercise. You will be given the Bayer Next Link glucometer to monitor BG levels throughout the evening and night. Visit 3 and 4 will be circuit type exercises (e.g. jumping jacks, plank, squats, etc.) for ~40 minutes. These visits are usually completed on the following week (after visit 1 and 2).

The participants will be fitted with a CGM that will provide constant real-time measurements of blood glucose values. The CGM may cause some discomfort upon insertion. This is a small glucose sensor that is inserted superficially into the surface of the skin and this will be done by the lead nurse practitioner. Since all of the participants that will be recruited will be insulin pump users, they will already have prior experience inserting an infusion set which also uses a needle under the surface of the skin. The CGM insertion will likely be a similar sensation as the infusion set, with a slight tingling upon insertion that stops immediately once inserted. The CGM will remain taped to the skin for the remainder of the experimental protocol (5-6 days). To make the CGM insertion more comfortable, participants will be given the option to insert the sensor with an auto-insertion device if they have done so in the past and prefer this option. This plastic device is used specifically with the CGM to make the insertion pain-free. The principal investigator (Dr. Michael Riddell) has extensive experience providing suggestions on proper insertion if necessary.

Participants will also be fitted with a lifestyle assessment system sports armband (Metria IH1, Vancive USA) that will be placed on the surface of the skin on the left upper portion of the arm. The principal student investigator (PSI) will apply this armband on the participant and it will remain on the skin for one week. Participants may do all of their regular physical activity and shower with the device and it will be returned to the PSI at the end of the week. The data from the CGM and the sports armband will be collected and uploaded on a computer and sent out to the participant for a detailed review of the data.

Risks and Discomforts: There are some mild to moderate risks associated with the participation of this study. Exercise can be associated with cardiovascular adverse events in very rare circumstances in the general population (angina, heart attack) and people with diabetes have a higher risk for cardiovascular disease compared with non-diabetics. A recent evidence-based review paper (Riddell & Burr, 2011) has shown; however, that the risk of a life-threatening event temporally associated with (or attributable to) exercise for people with T1DM is not different for the general population. Nonetheless, as a safety precaution, we will screen all participants for exercise readiness using the PAR-Q+ screening tool for individuals with metabolic diseases. During all visits, blood pressure and heart rate will be monitored throughout exercise using a bioharness (Zephyr Technology Corporations, USA) and the criteria for exercise test termination will follow the Canadian Society for Exercise Physiologists Clinical Practice Guidelines.

All of the investigators are certified in First Aid & CPR and are able to provide assistance if necessary. The subjects will not be eligible to participate if any heart condition exists. Should a medical emergency arise, University procedures will take place. Steps include calling 911 and providing the following information: location of the building (126 Bethune College), exact location of ill person, describe the nature and severity of the medical problem, and provide your name (Dessi Zaharieva) and telephone number (416-893-1697). York University Security Services will be contacted at ext. 33333 or (416) 736-5333 to be informed of why 911 was contacted. The emergency personnel will be met by PI and PSI at the entrance to Bethune College.

Other more common but less serious risks of exercise do exist with this population. With type 1 diabetes individuals during exercise, there is an increased risk of hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar). Fluctuations in BG levels are common during exercise, and hypoglycemia often occurs with endurance-type exercises. Hypoglycemia may cause dizziness, fatigue, shakiness, and/or tingling in the limbs. In this study, capillary glucose will be monitored ~every 15 minutes and volunteers will also wear a continuous interstitial glucose monitor (iPro, Medtronic, Canada). Dextrose will be supplied to all subjects prior to the onset of exercise and this will likely prevent any drastic reductions in BG levels. Since BG concentrations are being monitored so frequently, investigators will be able to notice hypoglycemic trends developing long before they place the individual at risk for any adverse event associated with severe hypoglycemia. If BG or interstitial glucose drops below 3.5 mmol/L, the exercise will be terminated immediately and additional "fast-acting" carbohydrate will be given orally (Dex4, AMG Medical, USA).

Similarly, the CGM may cause some discomfort upon insertion. This is a small glucose sensor that is inserted into the surface of the skin by yourself or the investigator (Dr. Michael Riddell) if required. Since all of the diabetic subjects that will be recruited will be insulin pump users, you will already have prior experience inserting an infusion set which also uses a needle under the surface of the skin. The CGM insertion will likely be a similar sensation as the infusion set, with a slight tingling upon insertion that stops once inserted. The CGM will remain taped to the skin for the remainder of the experimental protocol. To make the CGM insertion more comfortable, you will be given the option to insert the sensor with an auto-insertion device. This plastic device is used specifically with the CGM to make the insertion pain-free. The principal investigator (Dr. Michael Riddell) and principal student investigator (Dessi Zaharieva) have extensive experience inserting these devices and can provide tips on proper insertion if necessary.

During the VO_{2max} test and exercise sessions, you will be wearing a mouthpiece while running on the treadmill and this may be slightly uncomfortable, as breathing may feel slightly restricted. The exercise sessions should be more comfortable for the participants since the initial VO_{2max} measurements will be complete and subjects will know the feeling of the mouthpiece during exercise. With a V_{O2max} test, you will be running on a treadmill until you reach exhaustion. You may experience some symptoms of fatigue, nausea, and dizziness, but the may terminate the run if you feel that you have reached exhaustion.

Benefits of the Research and Benefits to You: You will complete a VO_{2max} at not cost and learn more about your physical fitness. A VO_{2max} test would normally cost $100 to complete outside of the research setting.

Participants will also have the benefit of wearing this new armband technology called Metria IH1 (Vancive, USA) that collects and reports physical activity, activity level, calories burned, sleep duration and quality, and more. The sports armband will not cause any immediate benefit to participants, but once the data is collected, it will be interesting to view. It is important to keep a careful record of activities performed, carbohydrates consumed, and insulin administration in order to understand the cause for observed alterations in blood glucose concentrations. By identifying any recurring trends, participants may subsequently identify changes that should be made to their management techniques.

Voluntary Participation: Your participation in the study is completely voluntary and you may choose to stop participating at any time. Your decision not to volunteer will not influence the treatment you may be receiving or the nature of your relationship with York University either now, or in the future.

Withdrawal from the Study: You can stop participating in the study at any time, for any reason, if you so decide. Your decision to stop participating, or to refuse to answer particular questions, will not affect your relationship with the researchers, York University, or any other group associated with this project. In the event you withdraw from the study, all associated data collected will be immediately destroyed wherever possible.

Confidentiality: All information you supply during the research will be held in confidence and unless you specifically indicate your consent, your name will not appear in any report or publication of the research. The data will be collected partially via handwritten notes (VO_{2max} data, blood glucose concentrations, and questionnaires), and digital data (CGM, blood glucose concentrations in excel, and polar heart rate data, etc. in excel). The data will be archived in a locked facility in 225B Lumbers laboratory. Confidentiality will be provided to the fullest extent possible by law. All of the hard copies of data will be kept in a safe and secure filing cabinet in the laboratory of Dr. Michael Riddell. Only the principal investigator (PI) and principal student investigator (PSI) will have access to these files. All of the electronic files will be collected on a personal laptop with password protection. Subject identifiers will be collected (participant names, phone number, and email) in order to contact the subjects for testing purposes. The participants names will be coded and only the PI and PSI will have access to this master list in order to keep the data anonymous. Upon publication of data (or after 5 years), the hard copies and electronic data will be destroyed.

Questions About the Research? If you have questions about the research in general or about your role in the study, please feel free to contact Dr. Mike Riddell either by telephone at (416) 736-2100, extension 22324 or by e-mail (mriddell@yorku.ca). This research has been reviewed and approved by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. If you have any questions about this process, or about your rights as a participant in the study, please contact the Sr. Manager & Policy Advisor for the Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone 416-736-5914 or e-mail ore@yorku.ca).

Legal Rights and Signatures:

I_____ *(insert your name),* consent to participate in the study "adjusting insulin pump basal levels for exercise in youth and adults with type 1 diabetes." conducted by Dessi Zaharieva. I have understood the nature of this project and wish to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Signature_____ **Date**_____
Participant

Signature_____ **Date**_____
Principal Investigator

Thank you for your assistance in this project. Please keep a copy of this form for your records.

Informed Consent Form 2

Date: _____

Project Title: OmniPod® **T**ype 1 diabetes **I**nsulin **M**anagement for **E**xercise study (Omni-TIME-study)

Principal Investigators:
Dr. Michael Riddell, Ph.D. (Professor)

Principal Student Investigator:
Dessi Zaharieva (Ph.D. Candidate, 2014)

Dr. Veronica Jamnik, Ph.D. (Associate Professor)

Purpose of the Research: The purpose of this study is to determine the effectiveness of three different basal insulin management strategies to reducing blood glucose during prolonged aerobic exercise in adults with type 1 diabetes (T1D). All participants will be using an OmniPod® (Insulet Corporation, USA) insulin pump. The OmniPod® is a Health Canada approved tubing-free insulin pump device that uses an insulin delivery 'pod' and a Personal Diabetes Manager (PDM). The PDM is a wireless handheld device that programs the pod, captures diabetes management events (food, exercise, etc.), and acts as a glucose meter (Abbott Freestyle, USA). The project will be carried out at York University in the Clinical Human Exercise Laboratory under the supervision of Dr. Michael Riddell. The overall goal of this research is to increase the percent time spent in target range during exercise and in recovery.

This research will be presented at conferences in the future, although no specific conference has been selected at this time. We also aim to publish this data in an academic journal, and share the information with the companies involved (OmniPod®, Insulet Corporation, USA, Abbott Freestyle, USA, etc.). All participants will remain anonymous.

What You Will Be Asked to Do in the Research: A total of four sessions will be required for this project. All visits will be carried out at York University in the Clinical Human Exercise Laboratory, located at Stong room 108. The first visit will be a familiarization session that requires completed informed consent, anthropometric measurements, continuous glucose monitor (CGM) connection, medical history questionnaire, PAR-Q Plus questionnaire, physical fitness assessment, and an initial VO_2max test. This session is estimated to take approximately 1.5 hours. The subsequent sessions will be three experimental trials of prolonged, steady state aerobic exercise, lasting 75 minutes. The experimental sessions (three) will require a bioharness strapped around the chest to measure physiological variables including heart rate, energy expenditure, etc. and finger capillary blood glucose (BG) measurements. These sessions will take ~2 hours each to complete.

Baseline/Screening Session (Visit 1): During this session, you will be asked to complete the medical history questionnaire and informed consent. A Physical Activity Readiness Questionnaire (PAR-Q+) will also be conducted to measure your pre-exercise health. An example of a question on the PAR-Q+ questionnaire includes: "Has your doctor ever said that you have a heart condition or high blood pressure: Yes or No". You will then have your height, weight, and body fat measured. An investigator of the same sex will conduct your measurements of body fat using skinfold calipers and this will be done in a private room. You will also be asked to complete a test of your maximal oxygen consumption (VO_2max) by running on a treadmill while the speed and incline are increased every 2 minutes until you reach exhaustion. You will be asked to refrain from drinking caffeinated beverages or ingesting caffeine supplements for the day of each experimental trial.

Experimental Sessions (Visit 2-4): You will be assigned to a sequence of the three experimental visits through a randomization process. Each exercise session will be separated by at least three days and you will be expected to complete all sessions within ~12 weeks from the time of the baseline/screening visit. Upon arrival to the laboratory, you will be asked to prick your own finger using your own lancing device. You will be given the Abbott Freestyle PDM to monitor BG levels and carbohydrate intake throughout the study. During each of the three exercise sessions, a basal rate adjustment will be made before the exercise. The three insulin strategies include:

(1) Control Strategy: -100% of usual basal rate at the start of exercise (i.e. pump suspension)
(2) Strategy 2: -50% of usual basal rate, set 90 minutes pre-exercise for the duration of exercise
(3) Strategy 3: -80% of usual basal rate, set 90 minutes pre-exercise for the duration of exercise

The exercise will consist of four 15 minute bouts of jogging at 50-60% of the participant's pre-determined aerobic capacity, separated by three 5 minute breaks (to simulate what is typically done in most team and individual workouts and sports). Regular finger capillary BG samples will be collected during exercise. In all three sessions, aerobic exercise (brisk walking/light jogging) will be performed in the post-absorptive state, ~4 hours after the last meal with their usual bolus insulin given.

You will be provided with a CGM (Dexcom™, USA) for the duration of the study and asked to insert the CGM one day before the first experimental session. If participants have never worn a CGM (Dexcom™, USA), they will have the option to wear one starting the initial screening visit for 7 days. The CGM will provide constant real-time measurements of BG values. The CGM may cause some discomfort upon insertion. This is a small glucose sensor that is inserted superficially under the surface of the skin and the lead investigator will do this. Since all of the participants that will be recruited will be insulin pump users, they will already have prior experience inserting a small needle into the skin. The CGM insertion will likely be a similar sensation as the 'pod' insertion, with a slight tingling upon insertion that stops immediately once inserted. The CGM will remain taped to the skin for the remainder of the experimental protocol (2-3 weeks). The principal investigator (Dr. Michael Riddell) has extensive experience providing suggestions on proper insertion if necessary.

Exercise intensity will be monitored continuously using heart rate and activity monitors. You will be fitted with a lifestyle assessment system sports armband (Metria IH1^{TM}, Vancive, USA) that will be placed on the surface of the skin on the upper portion of the non-dominant arm. The principal student investigator (PSI) will apply this armband on your arm and it will remain on the skin for one week. You may do all of your regular physical activity and shower with the device and it will be returned to the PSI at the end of the week. An accelerometer chest band (Zephyr^{TM} bioharness, USA) will also be strapped around your chest during exercise to monitor heart rate and removed at the end of each session. The data from the CGM and the sports armband will be collected and uploaded on a computer and sent out to the you for a detailed review of the data.

Following each exercise session, you will rest for 30 minutes and then consume a standardized meal (~50 g of carbohydrate, ~17g protein and ~8g of fat, Lean Cuisine^{TM}). The amount of bolus insulin given at the post-exercise meal will be based on the carbohydrate content of the meal and your own individualized insulin-to-carbohydrate ratio, insulin sensitivity index, and glycemic targets on your OmniPod® PDM. Insulin "corrections" will be given based on the patient's own OmniPod® settings (i.e. usual care). You will be asked to administer your bolus insulin 10-minutes before the start of consuming the meal. If hypoglycemia occurs prior to the meal (BG $\leq$ 3.9 mmol/L), you will be treated with 16 grams of fast acting carbohydrate (Dex4, AMG Medical) prior to the meal consumption.

You will be monitored for approximately two hours after the standardized meal prior to discharge. CGM monitor low- and high-glucose 'alerts' will be activated. You will also be instructed to perform a standardized basal rate reduction overnight to help reduce the risk of post-exercise nocturnal hypoglycemia (-20% from bedtime for 6 hours). Fingerstick BG will be collected ~ every 30-minutes in recovery and upon completion, will be sent home.

Inclusion Criteria

- Clinical diagnosis of presumed autoimmune type 1 diabetes, receiving daily insulin
- Last A1C $\leq$ 9.9%
- Age: 17-65 years
- Duration of T1D: $\geq$ 2 years
- Using CSII via OmniPod for at least 1 month (~50:50 bolus basal insulin ratio and on at least .25 units of insulin per kilogram body mass per day)
- Body mass index (BMI) <30 kg/m^2
- In good general health with no conditions that could influence the outcome of the trial, and in the judgment of the investigator is a good candidate for the study based on review of available medical history, physical examination and clinical laboratory evaluations
- Willing to adhere to the protocol requirements for the duration of the study

Exclusion Criteria

- Physician diagnosis of active diabetic retinopathy (proliferative or hemorrhage in past 6 months) that could potentially be worsened by exercise
- Physician diagnosis of peripheral neuropathy with insensate feet
- Physician diagnosis of autonomic neuropathy
- Medications:
    a. Beta-blockers

b. Agents that affect hepatic glucose production such as beta adrenergic agonists, xanthine derivatives
c. Pramlintide
d. Any other hypoglycemic agent

- Participation in other studies involving administration of an investigational drug or device at the time of screening for the current study or planning to participate in another such study during participation in the current study
- Severe hypoglycemic event defined as the individual requiring a third party or hospitalization in the last 3 months

Risks and Discomforts: There are some mild to moderate risks associated with the participation of this study. Exercise can be associated with cardiovascular adverse events in very rare circumstances in the general population (angina, heart attack) and people with diabetes have a higher risk for cardiovascular disease compared with non-diabetics. A recent evidence-based review paper (Riddell & Burr, 2011) has shown; however, that the risk of a life-threatening event temporally associated with (or attributable to) exercise for people with T1D is not different for the general population. Nonetheless, as a safety precaution, we will screen all participants for exercise readiness using the PAR-Q+ screening tool for individuals with metabolic diseases. During all visits, heart rate will be monitored throughout exercise using the Zephyr^{TM} bioharness and the criteria for exercise test termination will follow the Canadian Society for Exercise Physiologists Clinical Practice Guidelines.

All of the investigators are certified in First Aid & CPR and are able to provide assistance if necessary. Individuals will not be eligible to participate if any heart condition exists. Should a medical emergency arise, University procedures will take place. Steps include calling 9-1-1 and providing the following information: Location of the building (Stong room 108), exact location of ill person, describe the nature and severity of the medical problem, and provide your name (Dessi Zaharieva) and telephone number (416-893-1697). York University Security Services will be contacted at ext. 33333 or (416) 736-5333 to be informed of why 911 was contacted. The PI and PSI will meet the emergency personnel at the entrance to Stong College.

Other more common but less serious risks of exercise do exist with this population. With T1D individuals during exercise, there is an increased risk of hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar). Fluctuations in BG levels are common during exercise, and hypoglycemia often occurs with endurance-type exercises. Hypoglycemia may cause dizziness, fatigue, shakiness, and/or tingling in the limbs. In this study, BG will be monitored frequently and you will also wear a CGM that displays constant glucose values. Dextrose tablets (Dex4, AMG Medical, USA) will be available to all participants if needed at any time. Since BG concentrations are being monitored so frequently, investigators will be able to notice hypoglycemic trends developing long before they place the individual at risk for any adverse event associated with severe hypoglycemia. If BG or interstitial glucose drops below 3.9 mmol/L, the exercise will be terminated immediately and additional fast-acting carbohydrate will be given orally.

Similarly, the CGM may cause some discomfort upon insertion. This is a small glucose sensor that is inserted into the surface of the skin by yourself or the investigator (Dr. Michael Riddell) if required. Since all of the participants that will be recruited will be insulin pump users, they will already have prior experience inserting an infusion set which also uses a needle under the surface of the skin. The CGM insertion will likely be a similar sensation as the pod, with a slight tingling upon insertion that stops once inserted. The CGM will remain taped to the skin for the remainder of the experimental protocol. The principal investigator (Dr. Michael Riddell) and principal student investigator (Dessi Zaharieva) have extensive experience inserting these devices and can provide tips on proper insertion if necessary.

During the VO_2max test and exercise sessions, you will be wearing a mouthpiece while running on the treadmill and this may be slightly uncomfortable, as breathing may feel slightly restricted. The exercise sessions should be more comfortable for you once the initial VO_2max is complete because you will already know the feeling of the mouthpiece during exercise. With a VO_2max test, you will be running on a treadmill until you reach exhaustion. Participants may experience some symptoms of fatigue, nausea, and dizziness, but may terminate the run if you feel that you have reached exhaustion.

Benefits of the Research and Benefits to You: You will complete a VO_2max at no cost and learn more about your physical fitness. A VO_2max test would normally cost $100 to complete outside of the research setting.

Participants will also have the benefit of wearing this armband technology (Metria IH1™, Vancive, USA) that collects and reports physical activity, activity level, calories burned, sleep duration and quality, and more. The sports armband will not cause any immediate benefit to participants, but once the data is collected, it will be interesting to view. It is important to keep a careful record of activities performed, carbohydrates consumed, and insulin administration in order to understand the cause for observed alterations in BG concentrations. By identifying any recurring trends, participants may subsequently identify changes that should be made to their management techniques.

Voluntary Participation: Your participation in the study is completely voluntary and you may choose to stop participating at any time. Your decision not to volunteer will not influence the treatment you may be receiving or the nature of your relationship with York University either now, or in the future.

Withdrawal from the Study: You can stop participating in the study at any time, for any reason, if you so decide. Your decision to stop participating, or to refuse to answer particular questions, will not affect your relationship with the researchers, York University, or any other group associated with this project. In the event you withdraw from the study, all associated data collected will be immediately destroyed wherever possible.

Confidentiality: All information you supply during the research will be held in confidence and unless you specifically indicate your consent, your name will not appear in any report or publication of the research. The data will be collected partially via handwritten notes (VO_2max data, blood glucose concentrations, and questionnaires), and digital data (CGM, blood glucose concentrations in excel, and polar heart rate data, etc. in excel). The data will be archived in a locked facility in 225B Lumbers laboratory. Confidentiality will be provided to the fullest extent possible by law. All of the

hard copies of data will be kept in a safe and secure filing cabinet in the laboratory of Dr. Michael Riddell. Only the principal investigator (PI) and principal student investigator (PSI) will have access to these files. All of the electronic files will be collected on a personal laptop with password protection. Subject identifiers will be collected (participant names, phone number, and email) in order to contact the subjects for testing purposes. The participants names will be coded and only the PI and PSI will have access to this master list in order to keep the data anonymous. Upon publication of data (or after 5 years), the hard copies and electronic data will be destroyed.

Questions About the Research? If you have questions about the research in general or about your role in the study, please feel free to contact Dr. Mike Riddell either by telephone at (416) 736-2100, extension 22324 or by e-mail (mriddell@yorku.ca). This research has been reviewed and approved by the Human Participants Review Sub-Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. If you have any questions about this process, or about your rights as a participant in the study, please contact the Sr. Manager & Policy Advisor for the Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone 416-736-5914 or e-mail ore@yorku.ca).

Legal Rights and Signatures:

I _____ *(insert your name),* consent to participate in the study *"**Omni**Pod® **T**ype 1 diabetes **I**nsulin **M**anagement for **E**xercise study (Omni-TIME-study)"* conducted by Dessi Zaharieva. I have understood the nature of this project and wish to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Signature _____ **Date** _____
Participant

Signature _____ **Date** _____
Principal Investigator

Thank you for your assistance in this project. Please keep a copy of this form for your records.

Appendix F: Additional tables, graphs, & individual data (Paper #1)

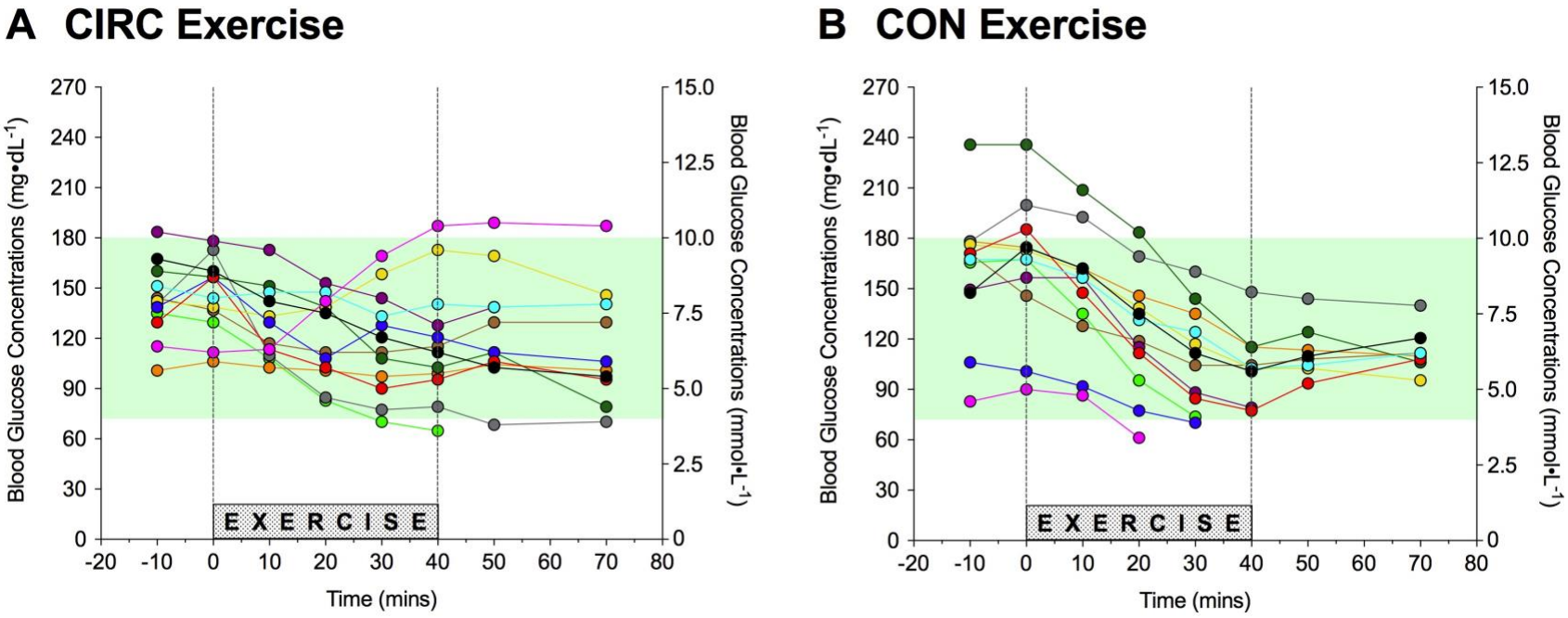


Figure F1: Individual blood glucose concentrations in CIRC vs. CON exercise.

A, CIRC suspended data. B, CON suspended data. Colour-coding represents each participant and the colour is carried out in both A and B. If hypoglycemia developed during activity, the exercise was terminated and participant was treated with dextrose tablets. Data points were carried out only until hypoglycemia developed. N=12.

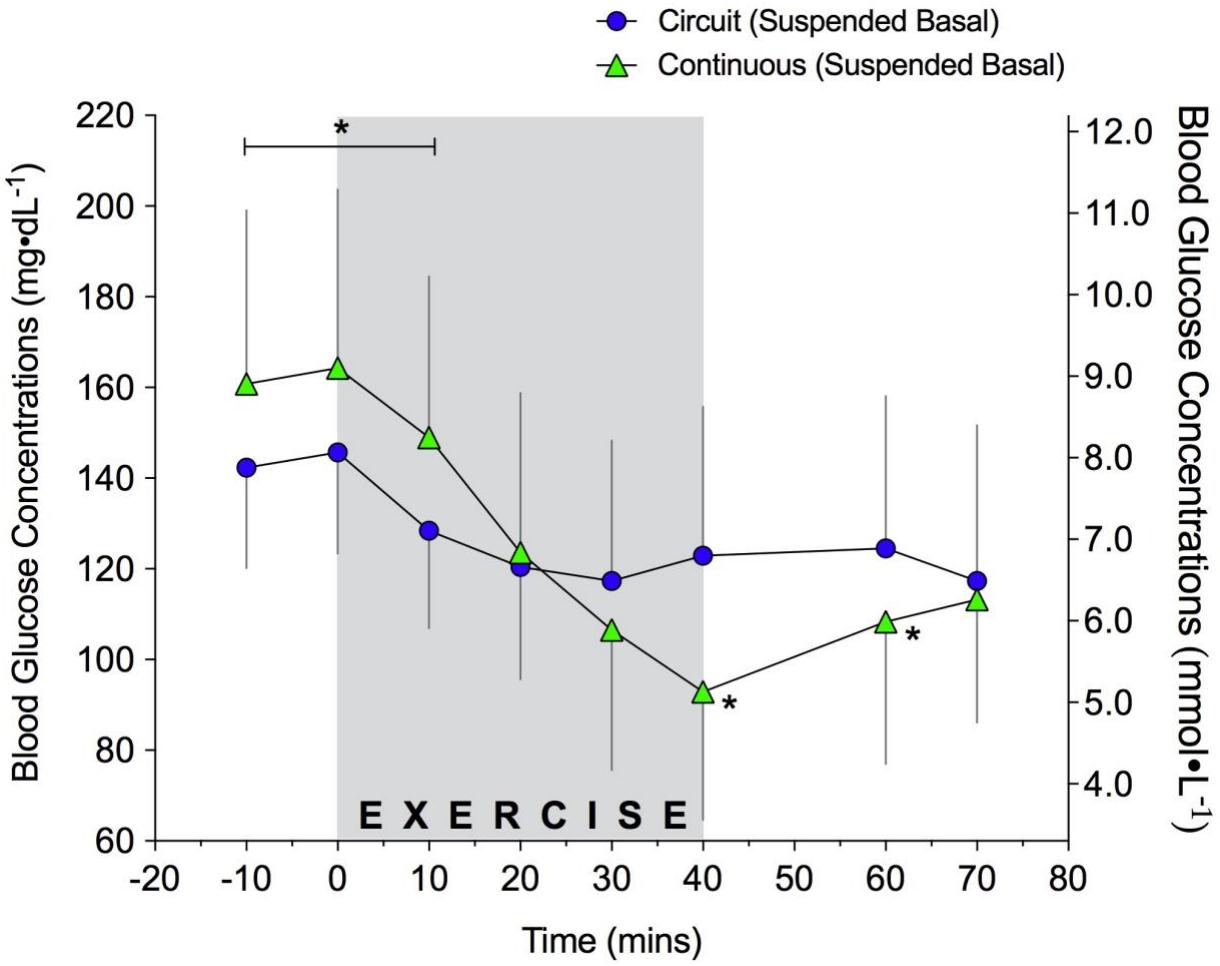


Figure F2: Absolute blood glucose concentration during CIRC and CON exercise.

Data represents CIRC (circle) and CON exercise (triangle) pre-, during, and post-exercise. Grey shading represents the exercise session (40-min). Data are expressed as mean ± SD, n = 12. * denotes significance of $P < 0.05$.

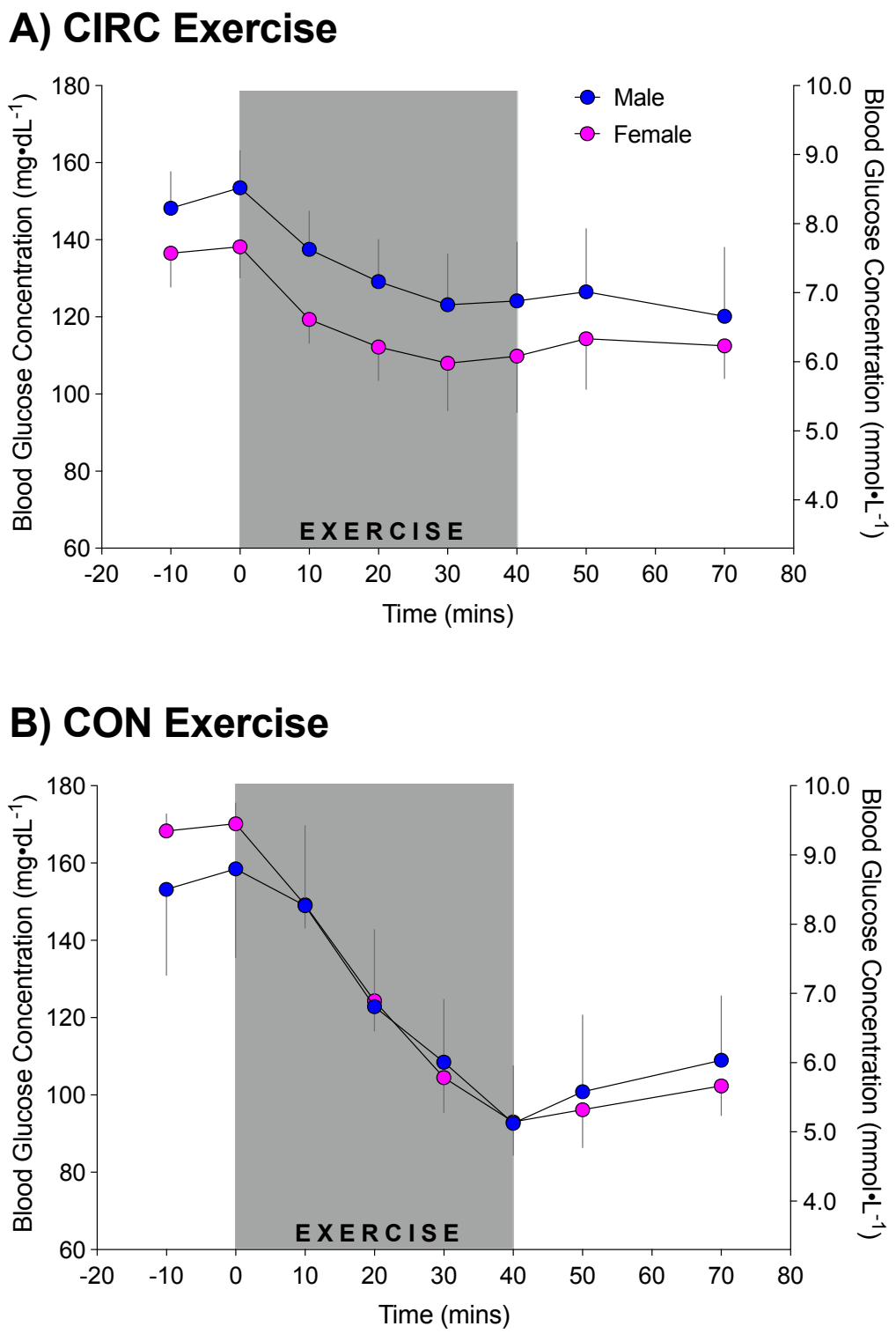


Figure F3: Male (blue) and female (pink) blood glucose levels during CIRC and CON exercise.

A, CIRC and B, CON. N = 6 males and 6 females. Data represents mean ± SEM.

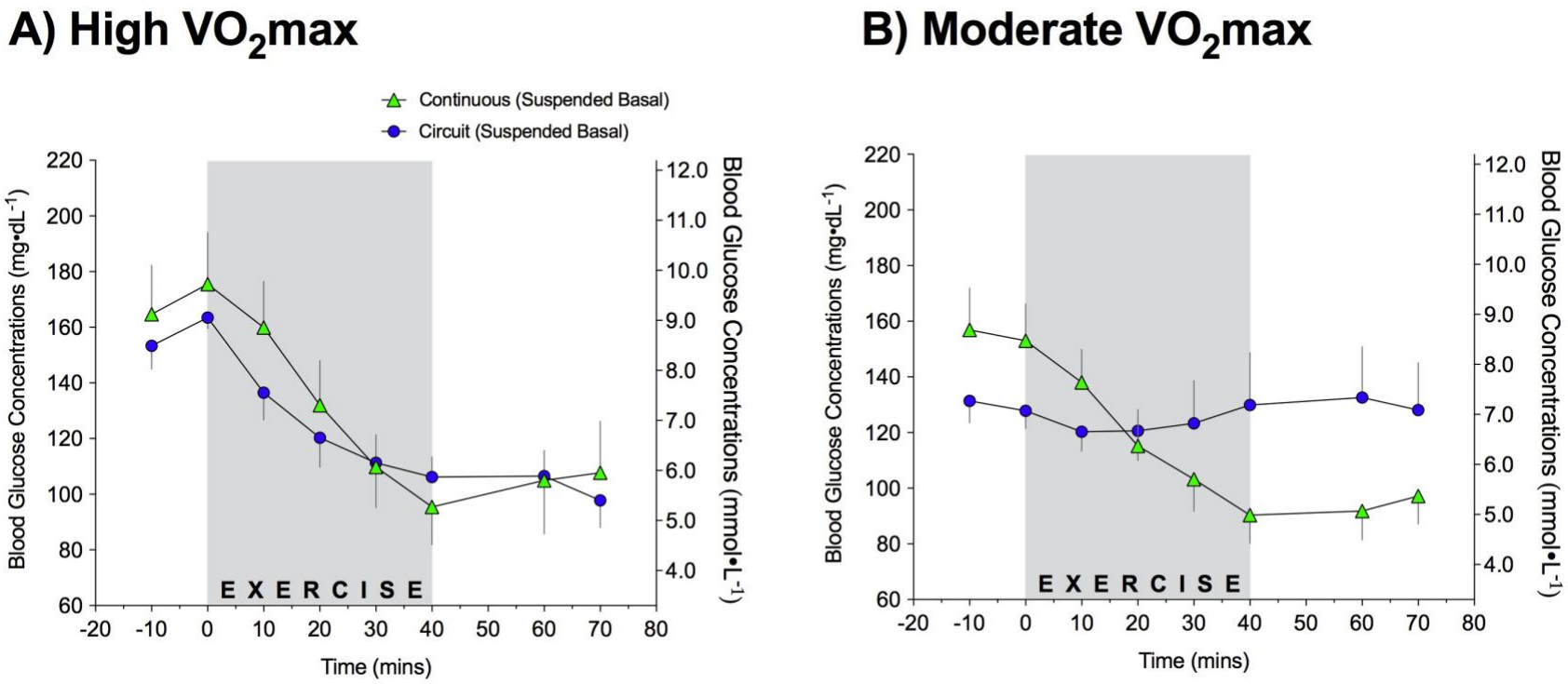


Figure F3: Absolute blood glucose concentration during CIRC and CON exercise separated by fitness level.

A, High VO_2max was > 48.0 mL/kg/min (n = 6) and B, Moderate VO_2max was < 42.0 mL/kg/min (n = 6). Data represents mean ± SD.

Appendix G: Additional tables, graphs, & individual data (Paper #2)

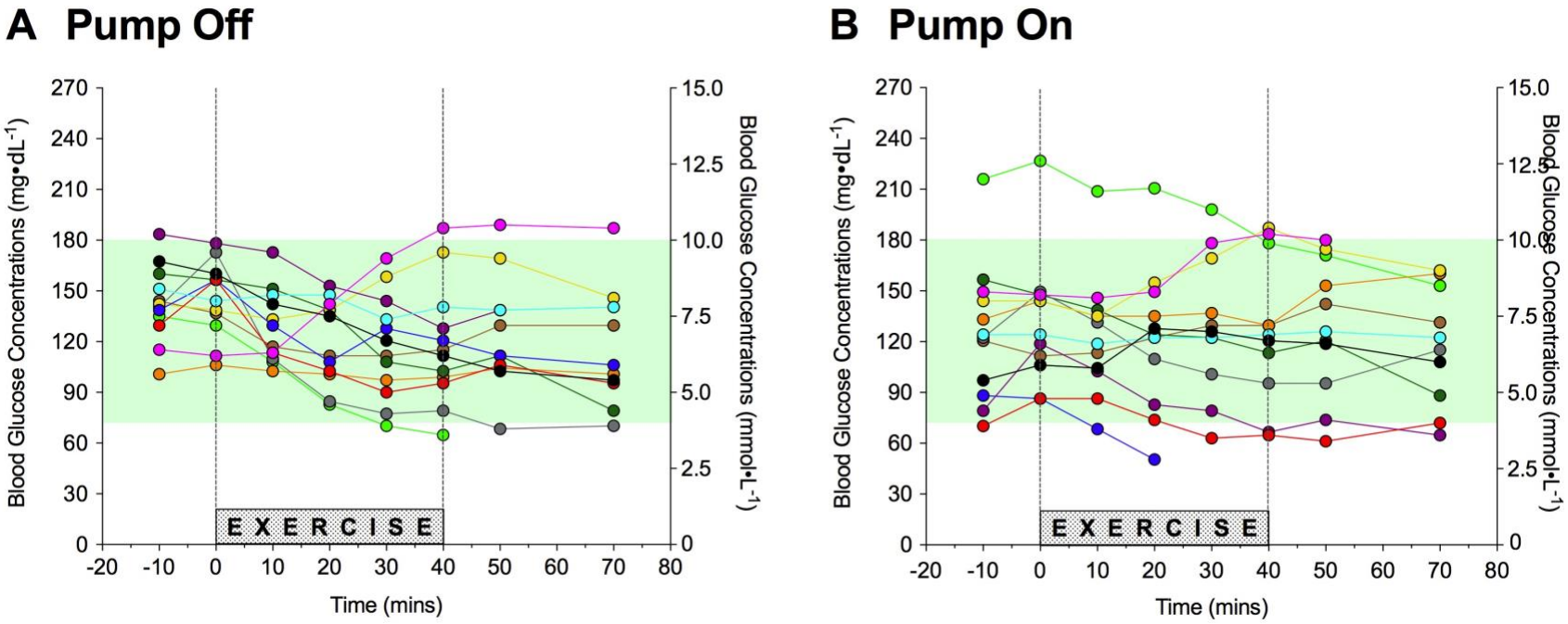


Figure G1: Individual glucose concentration during 'pump off' and 'pump on' exercise.

A, 'Pump off' exercise. B, 'Pump on' exercise. Colour-coding represents each participant and the colour is carried out in both A and B. If hypoglycemia developed during activity, the exercise was terminated and participant was treated with dextrose tablets. If hypoglycemia occurred, the data points show only until hypoglycemia developed. N=12.

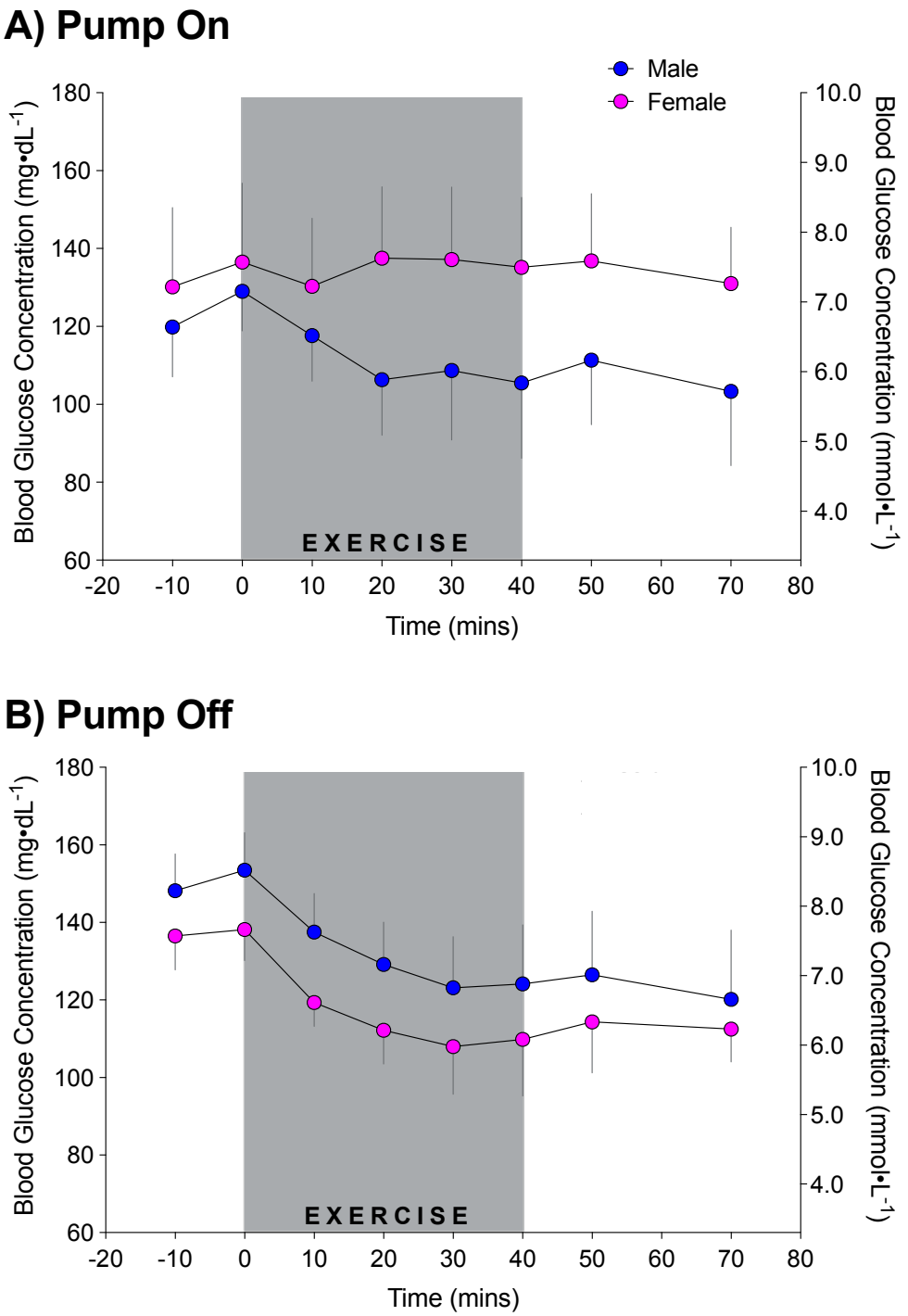


Figure G2: Male (blue) vs. female (pink) blood glucose concentrations in pump on and pump off exercise.

A, 'Pump on' and B, 'Pump off'. Total = 6 males and 6 females. Data represents mean ± SEM.

Appendix H: Additional tables, graphs, & individual data (Paper #3)

Subject ID	**Sex** (M/F)	**Age** (Years)	**Diabetes Duration** (Years)	**Insulin Type**	**TDD** (Units/kg)	**Weight** (kg)	**Height** (cm)	**BMI** (kg/m^2)	**Body Fat** (%)	**HbA_{1c}** (%)	**VO_2peak** (mL/kg/min)
Omni01	F	26	8	Novorapid	0.39	59.1	156	24.3	25.5	7.2	46.0
Omni02	M	27	5	Humalog	0.30	77.6	189	21.7	14.3	5.9	37.1
Omni03	F	28	3	Humalog	0.41	76.2	162	29.1	37.8	6.0	51.0
Omni04	M	50	34	Novorapid	0.39	78.4	184	23.2	18.1	6.6	59.2
Omni05	F	24	10	Novorapid	0.45	70.6	174	23.5	26.4	6.8	51.6
Omni06	F	30	16	Novorapid	0.44	68.8	163	26.0	33.8	6.3	41.6
Omni07	F	28	19	Novorapid	0.41	75.4	175	24.6	33.1	6.0	44.6
Omni08	F	25	3	Humalog	0.38	73.3	167	26.2	33.7	6.7	46.2
Omni09	F	57	25	Novorapid	0.42	71.0	170	24.6	33.9	7.0	37.5
Omni10	F	40	3	Humalog	0.65	46.4	151	20.3	23.1	7.0	31.6
Omni11	M	28	4	Novorapid	0.35	88.4	173	29.6	28.5	6.7	53.5
Omni12	F	22	6	Novorapid	0.58	76.8	168	27.2	36.5	6.6	49.3
Omni13	M	41	31	Novorapid	0.61	82.6	176	26.7	25.1	7.2	32.7
Omni14	F	19	7	Novorapid	0.25	75.2	162	28.5	37.0	5.9	42.9
Omni15	F	35	25	Novorapid	0.37	70.8	166	25.8	29.9	5.7	40.4
Omni16	F	24	12	Humalog	0.44	57.3	156	23.4	23.2	6.3	44.3
Omni17	F	28	21	Novorapid	0.54	71.4	167	25.6	32.3	6.0	49.1
Mean ± SD	**13 F 4 M**	**31 ± 10**	**14 ± 10**	**12 Novorapid 5 Humalog**	**0.43 ± 0.1**	**71.7 ± 9.9**	**168 ± 10**	**25.3 ± 2.5**	**29.0 ± 6.8**	**6.5 ± 0.5**	**44.6 ± 7.4**

Table H1: Individual baseline anthropometric and descriptive data of all study participants (n=17).

	80% BRR				50% BRR				Pump Suspension			
Subject ID	**VO_2**	**Relative VO_2**	**HR** (bpm)	**EE** (Kcal/min)	**VO_2**	**Relative VO_2**	**HR** (bpm)	**EE** (Kcal/min)	**VO_2**	**Relative VO_2**	**HR** (bpm)	**EE** (Kcal/min)
Omni01	22.4	54.1	129	7.50	21.7	52.4	133	7.55	21.6	52.2	133	8.10
Omni02	17.9	48.2	119	5.58	17.1	46.1	116	5.31	17.2	46.4	118	4.79
Omni03	21.7	48.4	118	6.89	21.5	48.0	118	6.38	21.8	48.7	119	6.93
Omni04	27.2	52.6	111	7.78	28.2	54.5	111	8.25	27.1	52.4	109	7.50
Omni05	25.3	55.2	119	8.16	27.1	59.2	130	8.8	26.0	56.8	126	8.80
Omni06	17.5	46.8	118	4.68	17.4	46.5	116	4.98	17.5	46.8	124	4.73
Omni07	20.1	50.1	115	6.56	21.8	54.4	123	6.69	20.2	50.4	111	5.30
Omni08	24.6	53.2	132	6.99	24.8	53.7	134	7.09	24.6	53.2	132	7.00
Omni09	19.3	51.5	100	5.52	20.2	53.9	99	5.77	20.3	54.1	100	7.13
Omni10	16.9	53.4	97	4.93	17.1	54.0	105	4.73	16.3	51.5	101	4.64
Omni11	24.0	49.9	130	7.62	23.3	48.4	133	6.65	23.9	49.7	139	6.96
Omni12	22.6	45.8	135	6.87	22.6	45.8	133	6.37	22.6	45.8	136	5.39
Omni13	14.5	48.2	124	4.62	15.0	49.8	131	4.77	14.8	49.2	124	4.19
Omni14	19.4	45.3	124	5.91	20.0	46.7	130	6.18	19.9	46.4	130	N/A
Omni15	18.6	46.1	135	5.88	19.8	49.1	135	N/A	20.9	51.8	138	N/A
Omni16	19.6	49.1	133	6.22	19.2	48.1	132	6.09	20.9	52.4	132	6.66
Omni17	20.8	47.7	127	5.95	20.8	47.7	132	6.61	22.1	50.7	138	6.80
Mean ± SD	**20.7 ± 3.33**	**49.8 ± 3.11**	**122 ± 11**	**6.33 ± 1.09**	**21.0 ± 3.52**	**50.5 ± 3.89**	**124 ± 11**	**6.39 ± 1.17**	**21.0 ± 3.33**	**50.5 ± 3.04**	**124 ± 13**	**6.33 ± 1.39**

Table H2: Relative exercise intensity, heart rate, and energy expenditure across all exercise conditions.
Data represented as mean ± SD, n = 17. HR = heart rate; EE = energy expenditure.

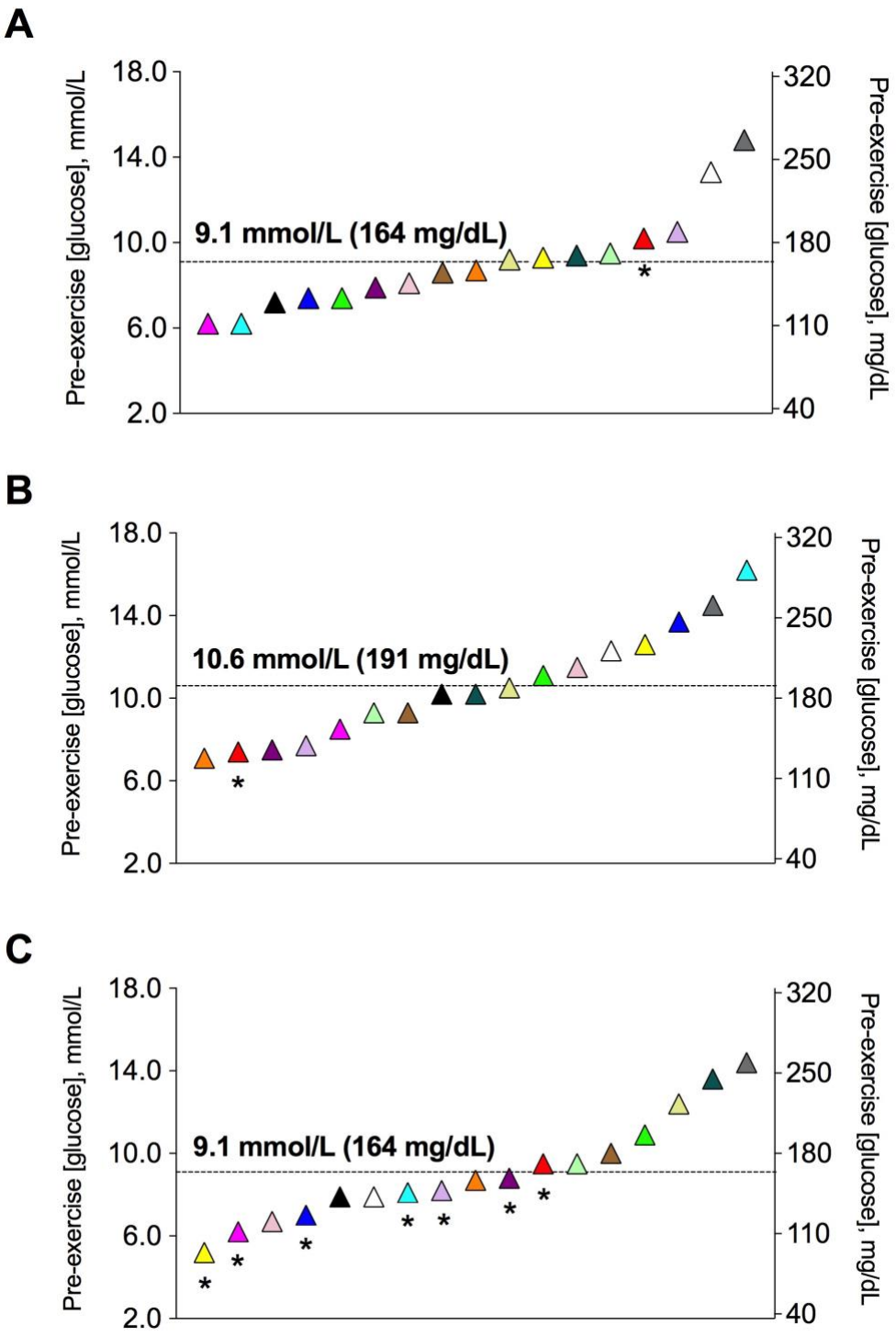


Figure H1: Individual and mean participant baseline blood glucose level for all exercise conditions.

A, 80% basal reduction; B, 50% basal reduction; C, pump suspension.

* denotes that hypoglycemia developed.

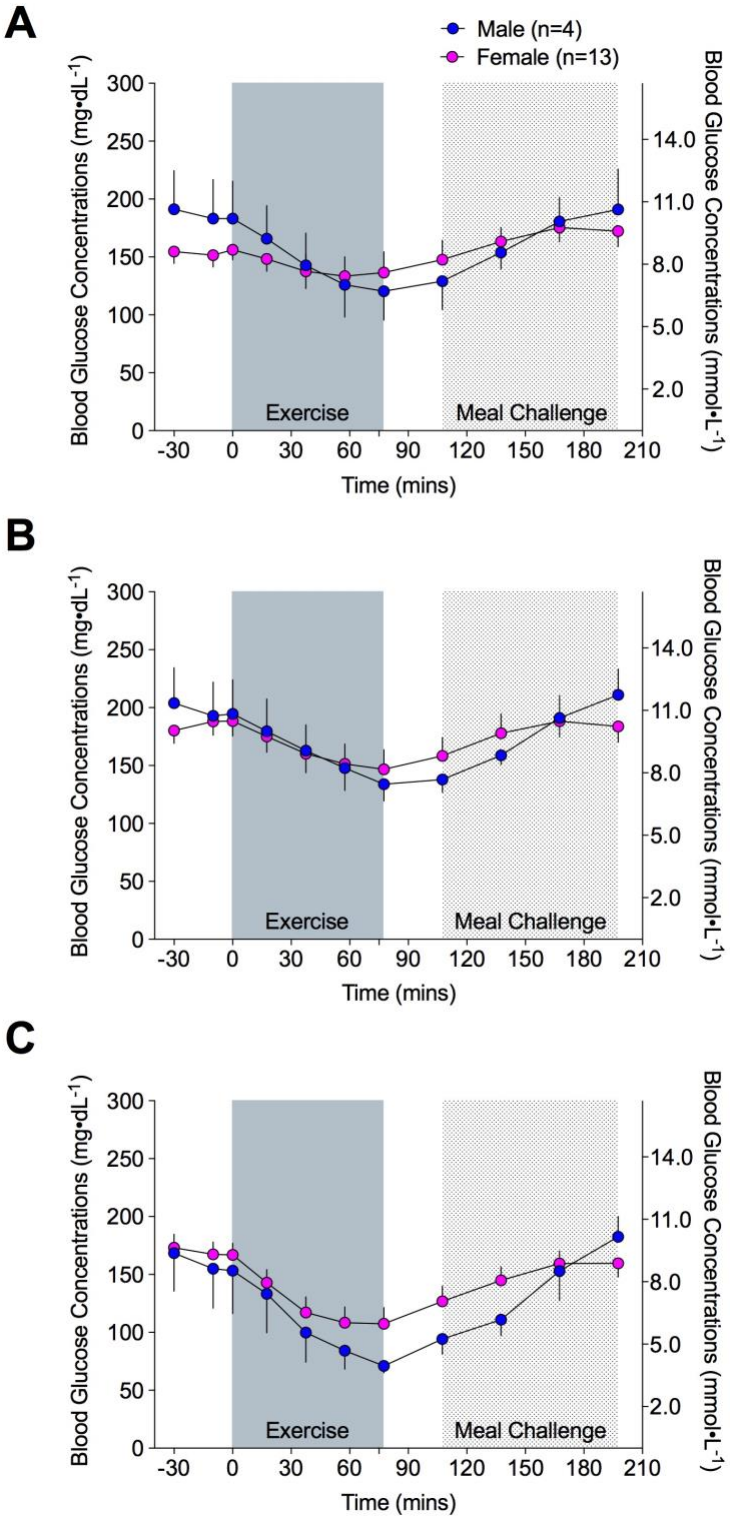


Figure H2: Male (blue) and female (pink) blood glucose levels across all exercise conditions. A, 80% BRR; B, 50% BRR; C, pump suspension.